

Study T-P106-141 ADME

Name of Company: TAP Pharmaceutical Products Inc Name of Finished Product: Dexlansoprazole MR Capsules Name of Active Ingredient: (+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole	
Title of Study: A Phase 1, Open-Label Study to Assess the Absorption, Distribution, Metabolism and Excretion of Orally Administered [¹⁴ C]Dexlansoprazole in Healthy Subjects	
Investigator: 1 investigator	
Study Center: 1 investigative site in the United States	
Publication (reference): None	
Study Period: Date of First Dose: 15 August 2006 Date of Last Procedure: 16 September 2006	Phase of Development: 1
Objective: The objective was to assess the absorption, distribution, metabolism, excretion, and safety of dexlansoprazole in healthy male subjects on Day 5 after administration of dexlansoprazole modified-release (MR) 60 mg once daily (QD) for 4 days followed by a single approximately 60 mg oral dose of [¹⁴ C]dexlansoprazole containing approximately 100 µCi of radioactivity on Day 5.	
Methodology: This was a Phase 1, single-center, open-label study in healthy male volunteers. Multiple doses of nonradiolabeled dexlansoprazole MR 60 mg were administered prior to administration of a single dose of approximately 60 mg radiolabeled dexlansoprazole. After signing the approved informed consent form, 6 adult male subjects aged 18 to 55 years, inclusive, in good health, and who satisfied the admission criteria, were selected to participate in this study. Subjects were confined to the clinic starting on Day -1 through potentially Day 12. Dexlansoprazole MR 60 mg capsule was administered at approximately 0900 hours on Days 1 through 4. On Day 5, approximately 60 mg dose of [¹⁴ C]dexlansoprazole containing approximately 100 µCi of radioactivity was administered as an oral preparation at about 0900 hours. Blood, urine, and fecal samples were collected from Day 5 to approximately Day 12 to determine the concentration of dexlansoprazole and its metabolites, and total radioactivity and metabolic profile of select samples containing sufficient radioactivity.	
Stability and radiopurity of [¹⁴ C]dexlansoprazole in Maalox was determined by high-performance liquid chromatography (HPLC) using a flow-through radioactivity detector. Plasma concentrations of dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone were determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay method. The lower limit of quantitation (LLOQ) values for dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone were 10.00, 1.00 and 2.00 ng/mL, respectively. Total radioactivity concentrations in plasma and urine, and oxidized whole blood and fecal homogenate samples were determined by liquid scintillation counting. Metabolite profiling and characterization of metabolites in plasma, urine, and feces were determined by radio-HPLC and liquid chromatography mass spectrometry (LC/MS) methods.	
Number of Subjects (Planned and Analyzed): Planned = 6, completed = 6, analyzed = 6.	
Diagnosis and Main Criteria for Inclusion: Healthy male subjects 18 to 55 years, inclusive.	

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Test Product, Dose and Mode of Administration, and Lot Numbers:					
Test Product	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Lot Number
Dexlansoprazole MR	one 60 mg capsule	60 mg QD on Days 1 to 4	Oral	Takeda Pharmaceutical Co Ltd	Z540R011
[¹⁴ C]Dexlansoprazole	approximately 60 mg (in a vial) containing approximately 100 µCi of radioactivity	approximately 60 mg QD in Maalox liquid on Day 5	Oral	(b) (4) (b) (4) (b) (4)	1613-1613-06-501
Duration of Treatment: Dexlansoprazole MR on Days 1 to 4 and [¹⁴ C]dexlansoprazole on Day 5.					
Reference Therapy, Dose and Mode of Administration, and Lot Number: Not applicable					
Criteria for Evaluation:					
Efficacy: Efficacy was not assessed in this study.					
Pharmacokinetics: Each subject's CYP2C19 metabolizer status, ie extensive metabolizer (EM), or poor metabolizer (PM) was established by genotyping a blood sample. Plasma pharmacokinetic parameters for total radioactivity, dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone were estimated using standard noncompartmental methods. Pharmacokinetic parameters included maximum (peak) plasma concentration (C _{max}), time to maximum (peak) drug concentration (t _{max}), apparent terminal elimination-rate constant (λ _z), apparent terminal elimination-phase half-life (t _{1/2z}), area under the plasma concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC _t) and AUC from time zero to 24 hours (AUC ₂₄), and the ratio of metabolite-to-dexlansoprazole AUC ₂₄ . Oral clearance (CL/F) and apparent volume of distribution during the terminal phase (V _z /F) were estimated for dexlansoprazole. Concentration of radioactivity in red blood cells was determined from whole blood and plasma concentrations and hematocrit values.					
Safety: Safety was monitored by assessing adverse events (AEs), concomitant medication use, clinical laboratory tests, physical examinations, vital signs, and 12-lead electrocardiograms (ECGs).					
Statistical Methods:					
Efficacy: Efficacy was not assessed in this study.					
Pharmacokinetics: Plasma concentrations of total radioactivity, dexlansoprazole, 5-hydroxy dexlansoprazole, and dexlansoprazole sulfone and their pharmacokinetic parameter estimates are tabulated with descriptive statistics. Whole blood and red blood cell (RBC) concentrations of total radioactivity are tabulated with descriptive statistics. For urine and feces, the percent total radioactivity recovered are calculated and tabulated with descriptive statistics.					
Safety: Adverse events that started after the first dose or worsened in severity were summarized. Adverse events were classified according to Medical Dictionary of Regulatory Activities (MedDRA) System Organ Class (SOC), High Level Term (HLT), and Preferred Term (PT), and were tabulated with a breakdown by event severity. Similar AE tabulations were performed on those events assessed by the investigator as related (possibly or definitely) to study drug. Baseline, postdose, and change from baseline to postdose values were summarized utilizing descriptive statistics.					

Statistical Methods:

Safety (Cont):

A table with predefined potentially clinically important (PCI) clinical laboratory variables was presented. If applicable, individual subject data with PCI clinical laboratory values were presented.

Vital signs were summarized by presenting descriptive statistics for baseline, upon rising Day 2 through Day 12, postdose on Day 5, and change from baseline upon rising on Day 12 or the last day of confinement. ECGs were summarized as well.

Summary and Conclusions:

Demographics:

Gender: Male 6 (100%); Race: Black 1 (17%) and White 5 (83%); Ethnicity: Not-Hispanic or Latino 6 (100%); Age: 26 ± 6.99 (range 20 to 39) years; Weight: 77.8 ± 7.47 (range 64 to 83) kg; Height: 176.1 ± 4.36 (range 168 to 180) cm.

Efficacy Results:

Efficacy was not assessed in this study.

Pharmacokinetic Results:

The phenotype of one subject enrolled in this study (Subject 106) was designated as a PM while the remaining 5 subjects (Subjects 101 to 105) were designated as EMs based on their CYP2C19 genotypes. A summary of noncompartmental pharmacokinetic parameter estimates for total radioactivity, dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone in plasma following a mean oral dose of 58.8 mg [^{14}C]dexlansoprazole containing 99.8 μCi in Maalox on Day 5 after 4 days of daily 60 mg dexlansoprazole MR doses follows:

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Summary and Conclusions:							
Pharmacokinetic Results (Cont):							
	t_{max} (h)	C_{max} (ng/mL)	AUC_{24} (ng-h/mL)	$t_{1/2}$ ^c (h)	CL/F (L/h)	V_z/F (L)	AUC_{24} Ratio (%) ^d
Total Radioactivity							
Mean All Subjects	1.50	1561.89	10051.22	11.90 (7.27)	NA	NA	NA
CV(%)	148	33	103	79	NA	NA	NA
Mean ^a (101-105)	0.60	1374.80	5861.85	12.38 (6.94)	NA	NA	NA
CV(%)	37	20	29	85	NA	NA	NA
Subject 106 ^b	6.00	2497.35	30998.04	9.51	NA	NA	NA
Dexlansoprazole							
Mean All Subjects	1.50	1176.17	6963.86	2.24 (1.64)	17.5	38.4	NA
CV(%)	148	42	123	86	68	50	NA
Mean ^a (101-105)	0.60	1001.40	3507.17	1.46 (1.43)	20.5	41.8	NA
CV(%)	37	27	46	15	50	46	NA
Subject 106 ^b	6.00	2050	24247.31	6.17	2.4	21.4	NA
5-Hydroxy Dexlansoprazole							
Mean All Subjects	1.21	54.35	198.00	2.28 (1.84)	NA	NA	7.4
CV(%)	116	68	56	66	NA	NA	94
Mean ^a (101-105)	0.65	64.62	231.56	1.68 (1.63)	NA	NA	8.8
CV(%)	52	47	35	20	NA	NA	76
Subject 106 ^b	4.00	2.97	30.21	5.26	NA	NA	0.1
Dexlansoprazole Sulfone							
Mean All Subjects	1.50	57.03	918.60	7.88 (2.40)	NA	NA	4.2
CV(%)	150	200	239	134	NA	NA	209
Mean ^a (101-105)	0.60	10.43	23.68	7.79 (2.10)	NA	NA	0.6
CV(%)	86	49	76	152	NA	NA	38
Subject 106 ^b	6.00	290.00	5393.20	8.34	NA	NA	22.2
NA: not applicable; CV = Coefficient of Variation. a Descriptive statistics for CYP2C19 extensive metabolizers (Subjects 101 to 105). b Individual values for Subject 106, CYP2C19 poor metabolizer. c Arithmetic mean (harmonic mean). d $(AUC_{24} \text{ metabolite}/AUC_{24} \text{ dexlansoprazole}) \times 100\%$.							
Recovery of total radioactivity in the 6 subjects ranged from approximately 92% to 103%, with a mean of approximately 98% by 168 hours postdose (7 days). Radioactivity was nearly evenly distributed in excreta with an overall mean recovery of approximately 51% in urine and approximately 48% in feces. Although there was only one CYP2C19 PM in this study, metabolizer status did not appear to have a major impact on recovery of radioactivity. The majority of circulating radioactivity was accounted for by dexlansoprazole in both EM and PM subjects. Contributions to total circulating radioactivity due to inactive metabolites, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone were low as were their relative concentrations compared to dexlansoprazole plasma concentrations. Most calculated RBC binding values were negative and therefore assigned a concentration of 0 ng eq/g indicating little or no partitioning of radioactivity into RBC's.							
Approximately 92% to 100% of the plasma radioactivity over 6 hours was identified. In addition to parent compound (major peak), 8 to 10 metabolites were detected in plasma. 5-Glucuronyloxy dexlansoprazole and 5-hydroxy dexlansoprazole were major metabolites in plasma from EMs (Subjects 101 through 105), with maximum mean percentages of approximately 10% and 6% of sample radioactivity, respectively at 1, 1.5, 3, and 4 hours. Dexlansoprazole sulfone was the major metabolite in plasma from Subject 106 (PM) with maximum							

Summary and Conclusions:**Pharmacokinetic Results (Cont):**

percentages of approximately 8% of sample radioactivity at 6 hours and increasing to approximately 23% at 16 hours.

Dexlansoprazole was not detected as a radioactive component in urine. Radioactivity excreted in urine consisted of at least 16 metabolites. Overall, approximately 81% to 94% of radioactivity excreted into urine as metabolites was tentatively identified. 5-Glucuronyloxy dexlansoprazole and 5-glucuronyloxy dexlansoprazole sulfide were major metabolites in EMs, accounting for approximately 12% to 16% and 10% to 12% of administered dose, respectively, through 24 hour postdose. 2-S-N-Acetylcysteiny benzimidazole was the major metabolite in urine from Subject 106 (PM) and accounted for 19% of dose through 24 hour postdose. The radioactivity excreted in the feces consisted of at least 7 metabolites, accounting for 64% to 75% of radioactivity. No apparent qualitative differences in the fecal metabolite profiles of radioactivity were noted between Subjects 101 to 105 (CYP2C19 EMs) and Subject 106 (CYP2C19 PM). The major radioactive peak present in each fecal homogenate profile accounted for approximately 17% to 28% of dose radioactivity. Tandem mass spectrometry (MS/MS) analysis of this peak from Subjects 101 and 103 showed both dexlansoprazole and 5-hydroxy dexlansoprazole sulfide and indicated that 5-hydroxy dexlansoprazole sulfide was the predominate component. Another major metabolite tentatively identified in feces of all subjects was dexlansoprazole sulfide which accounted for approximately 4.3% to 7.0% of the dose eliminated in feces.

Safety Results:

There were no deaths, or other serious AEs, and no subject withdrew from the study due to an AE. No subject experienced a new AE or worsening of an existing AE during the dosing period (dexlansoprazole MR on Days 1 to 4 and [¹⁴C]dexlansoprazole on Day 5). Two subjects experienced one AE each, 4 days after receiving [¹⁴C]dexlansoprazole (MedDRA PTs Abdominal Pain and Diarrhoea). These AEs were of mild severity and were considered by the investigator to be not related to study drug. In addition, no subject had laboratory values, physical examinations, vital signs, and ECGs that were considered by the investigator to be clinically significant or were reported as AEs.

Conclusions:

Following administration of approximately 60 mg oral dose of [¹⁴C]dexlansoprazole on Day 5 to 6 healthy male subjects, 98% of the dosed radioactivity was recovered in the excreta after 7 days postdose and with nearly equal distribution between urine and feces. In plasma, dexlansoprazole was the largest radioactive component detected, accounting for over 70% of the plasma radioactivity. Dexlansoprazole was metabolized by oxidation, reduction and conjugation to at least 19 metabolites in plasma, urine, and feces. In addition to parent compound, up to 10 metabolites were detected in plasma, with 5-glucuronyloxy dexlansoprazole and 5-hydroxy dexlansoprazole being the major metabolites. The radioactivity excreted in urine and feces consisted of up to 16 and 7 metabolites, respectively, with 5-glucuronyloxy dexlansoprazole and 5-glucuronyloxy dexlansoprazole sulfide being the major urinary metabolites, and 5-hydroxy dexlansoprazole sulfide and dexlansoprazole sulfide being the major fecal metabolites.

Oral administration of dexlansoprazole MR 60 mg capsules QD for 4 days and approximately 60 mg of [¹⁴C]dexlansoprazole as an oral preparation once on Day 5 did not show any safety concern in healthy subjects.

Study T-P104-122 Pharmacokinetics and pharmacodynamics

Name of Company: TAP Pharmaceutical Products Inc.				
Name of Finished Product: TAK-390MR				
Name of Active Ingredient: R-(+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole				
Title of Study: A Phase 1, Single-Center, Randomized, Open-Label, Three-Period Crossover, Multiple-Dose Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety Following Administration of Oral Doses of TAK-390MR (30 mg and 60 mg) and Lansoprazole 15 mg in Healthy Subjects				
Investigator(s) (b) (4)				
Study Center(s) (b) (4)				
Publication (reference): None				
Study Period: Date of First Dose: 11 November 2005 Date of Last Procedure: 30 January 2006			Phase of Development: 1	
Objective(s): The objectives of this study were to evaluate the pharmacokinetics and pharmacodynamics of TAK-390 and lansoprazole following a single dose (Day 1) and multiple doses (Day 5) of 30 mg or 60 mg of the modified-release formulation of TAK-390 (TAK-390MR) or 15 mg of lansoprazole delayed-release capsules and to evaluate the safety of 30 mg or 60 mg of TAK-390MR or 15 mg of lansoprazole during once daily (QD) oral administration for 5 consecutive days.				
Methodology: This was a Phase 1, randomized, open-label, single-center, multiple-dose, 3-period crossover study. Forty-five healthy subjects participated in the study and received a different dosing regimen during each period of the study, so that at study completion each subject had received all 3 regimens. The subjects were randomly assigned to a sequence which specified the order in which they received each of the 3 different regimens, as summarized in the following table.				
Regimen Sequences				
Sequence	Number of Subjects	Period 1	Period 2	Period 3
1	15	Regimen A	Regimen B	Regimen C
2	15	Regimen B	Regimen C	Regimen A
3	15	Regimen C	Regimen A	Regimen B
Regimen A: 30 mg of TAK-390MR administered QD for 5 consecutive days with 240 mL of water. Regimen B: 60 mg of TAK-390MR administered QD for 5 consecutive days with 240 mL of water. Regimen C: 15 mg of lansoprazole administered QD for 5 consecutive days with 240 mL of water.				
On Day -1 of each period, subjects were confined to the clinical testing facility, and they remained confined until all study procedures were completed on Day 6 of each period. During each period, dosing began at approximately 0900 hours on Days 1 through 5. A washout interval of at least 5 days separated the last dose of one period from the first dose of the consecutive period. Safety was monitored through adverse event reports, concomitant medication usage, 12-lead electrocardiograms (ECGs), physical examinations, vital sign assessments, and laboratory evaluations. The pharmacokinetic and pharmacodynamic profiles of TAK-390 administered as the modified-release formulation and of lansoprazole were assessed through blood sampling for pharmacokinetic analysis and intragastric pH monitoring for pharmacodynamic analysis.				
Number of Patients (planned and analyzed): 45 planned and enrolled; 43 subjects were included in the pharmacodynamic analyses; 43 and 45 subjects were included in the pharmacokinetic analyses for TAK-390 and lansoprazole, respectively; and 45 subjects were included in the safety analyses.				
Diagnosis and Main Criteria for Inclusion: Male and female subjects between 18 and 55 years of age, inclusive, in general good health.				

Test Product, Dose and Mode of Administration, Batch Number:				
Test Product	Dose	Mode of Administration	Lot Number	Manufacturer
TAK-390MR Capsules	30 mg	Oral	Z540A014	Takeda Pharmaceutical Company Limited
TAK-390MR Capsules	60 mg	Oral	Z540R011	Takeda Pharmaceutical Company Limited
Duration of Treatment: Each of the 3 crossover periods consisted of 5 consecutive days of dosing. A washout interval of at least 5 days separated the last dose of 1 period from the first dose of the consecutive period.				
Reference Therapy, Dose and Mode of Administration, Batch Number:				
Reference Product	Dose	Mode of Administration	Lot Number	Manufacturer
Lansoprazole Capsules	15 mg	Oral	282552E21	Takeda Pharmaceutical Company Limited
Criteria for Evaluation:				
Efficacy: Efficacy was not assessed in this study. However, the effects of TAK-390MR and lansoprazole on intragastric pH were assessed, as were the plasma drug concentration and pharmacokinetic parameters for TAK-390 and lansoprazole.				
Pharmacodynamics: Intragastric pH during the 24 hours after dosing was measured for each of the regimens on Days 1 and 5 of each period. The intragastric pH was evaluated using the average pH over the entire 24-hour postdose interval, as well as over the following intervals of time relative to dosing: 0-4 hours, >4-9 hours, >9-12 hours, >12-16 hours, and >16-24 hours. For these intervals, the percent of time that the intragastric pH was >3, >4, >5, or >6 was also determined.				
Pharmacokinetics: Plasma concentrations of TAK-390 or lansoprazole were determined, and pharmacokinetic parameters for TAK-390 or lansoprazole in plasma were estimated using standard noncompartmental methods. The pharmacokinetic parameters included the observed maximum plasma concentration (C_{max}); the time to reach the observed maximum plasma concentration (t_{max}); the apparent terminal-phase elimination rate constant (λ_z); the apparent terminal elimination half-life ($t_{1/2z}$); and the area under the plasma concentration versus time curve (AUC) from time zero to the time of the last measurable concentration (AUC_t), to 24 hours (AUC_{24} , Day 5 only), and to infinity (AUC_{∞} , Day 1 only). In addition, the oral clearance (CL/F) and apparent volume of distribution (V_z/F) for TAK-390 and lansoprazole were estimated.				
Safety: Safety was monitored by assessing adverse events, concomitant medication usage, clinical laboratory variables, physical examinations, ECGs, and vital signs.				
Statistical Methods:				
Efficacy: Efficacy was not assessed in this study.				
Pharmacodynamics: Descriptive statistics for each of the pharmacodynamic parameters were tabulated. For each of Days 1 and 5, the effect of the 3 dose regimens were compared using ANOVA models that included effects for sequence, subject nested within sequence, period and regimen. The analysis was carried out on mean pH and percent of time that pH exceeded 4 (based on 15-minute medians) during the 24-hour postdose interval and over each of the following intervals of time relative to dosing: 0-4 hours, >4-9 hours, >9-12 hours, >12-16 hours, and >16-24 hours. Within the ANOVA framework, pairwise comparisons of the regimens were performed.				

Pharmacokinetics:

For each regimen, TAK-390MR or lansoprazole plasma concentration data and pharmacokinetic parameter estimates were tabulated and descriptive statistics computed. The assessment of dose proportionality for the 2 regimens of TAK-390MR on each of Days 1 and 5 was performed via 90% confidence intervals for the ratios of the central values of C_{max} , AUC_t , and AUC_{∞} (Day 1) or AUC_{24} (Day 5) obtained within the framework of the ANOVA models. Pairwise comparisons of the pharmacokinetic parameters for TAK-390 between Day 1 and Day 5 were performed within each TAK-390MR regimen using paired t-tests.

Safety:

All subjects who received at least 1 dose of study drug were included in the analyses of safety. Treatment-emergent adverse events were summarized for each regimen and overall. Baseline, postdose, and mean change from baseline to postdose were summarized by regimen for clinical laboratory variables and for vital signs. Subjects with laboratory or vital sign results that met the predefined criteria for potentially concerning values were identified.

Summary-Conclusions:**Efficacy Results:**

Efficacy was not assessed in this study.

Pharmacodynamic Results:

Intragastric pH results for each regimen for the total 24-hour interval, along with the differences between regimens, are summarized in the following table.

Analysis of Intragastric pH Results						
pH Measure Study Day	Intragastric pH Result ^a for Each Dosing Regimen during the Total 24-hour Interval			Differences ^b (Significance) Between Dosing Regimens for the Total 24-hour Interval		
	A	B	C	A versus C	B versus C	A versus B
Mean Intragastric pH						
Day 1	3.34	3.64	2.63	0.71***	1.02***	-0.31**
Day 5	3.67	3.94	3.21	0.47***	0.74***	-0.27*
Percent of Time Intragastric pH Exceeded 4						
Day 1	45	52	30	16***	22***	-6*
Day 5	52	55	41	11***	14***	-3

Note: Regimen A = 30 mg of TAK-390MR, Regimen B = 60 mg of TAK-390MR, and Regimen C = 15 mg of lansoprazole

a The estimates of the mean are least squares means, which took into account the possibility of period effects.

b The differences presented are the differences in least squares means.

*, **, *** Indicate statistical significance at the $p = 0.05$, 0.01 , or 0.001 level, respectively.

For both Day 1 and Day 5, the TAK-390MR 30-mg and 60-mg regimens produced higher mean pH and greater percent of time pH exceeded 4 than did 15 mg of lansoprazole. Generally, the 60-mg TAK-390MR regimen resulted in higher mean pH and greater percent of time pH exceeded 4 than did the 30-mg TAK-390MR regimen, but this difference was less pronounced on Day 5 than on Day 1.

Pharmacokinetic Results:

Noncompartmental pharmacokinetic parameter estimates for TAK-390 or lansoprazole following oral administration of 30-mg or 60-mg doses of TAK-390MR or a 15-mg dose of lansoprazole are summarized in the following table.

Plasma Pharmacokinetic Parameter Estimates for TAK-390 or Lansoprazole Following Oral Administration of 30 mg or 60 mg of TAK-390MR or 15 mg of Lansoprazole QD for 1 or 5 Days

Regimen	Day	Measure	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng-h/mL)	AUC_{0-24}^a (ng-h/mL)	$t_{1/2z}^b$ (h)
A (30 mg of TAK-390MR)	1	N	44	44	44	43	43
		Mean	4.38	576.5	2893	2977	1.52
		CV%	38	54	51	50	NA
	5	N	44	44	44	43	43
		Mean	4.45	658.1	3182	3275	1.49
		CV%	37	40	49	47	NA
B (60 mg of TAK-390MR)	1	N	43	43	43	43	43
		Mean	4.59	1208	5885	5951	1.65
		CV%	36	46	46	46	NA
	5	N	43	43	43	41	41
		Mean	4.88	1388	6463	6400	1.69
		CV%	40	53	48	48	NA
C (15 mg of lansoprazole)	1	N	45	45	45	44	44
		Mean	1.67	423.9	1049	1082	1.30
		CV%	53	37	48	47	NA
	5	N	45	45	45	45	45
		Mean	1.63	402.2	1046	1076	1.34
		CV%	44	39	48	47	NA

a AUC_{0-24} for Day 1, AUC_{0-24} for Day 5

b Harmonic Mean

h = hour, NA = Not Applicable

The initiation of absorption of TAK-390 was rapid following oral administration of 30 mg or 60 mg of TAK-390MR. After this initial rapid drug-input phase, plasma TAK-390 concentrations declined until rising again and achieving C_{max} at approximately 4 to 5 hours (t_{max}) postdose. Apparent dose proportionality was observed for C_{max} and AUC following oral administration of 30 mg and 60 mg of TAK-390MR. Results of the statistical dose proportionality assessment supported this observation. In addition, the plasma exposure of TAK-390 on Day 5 was generally similar to that observed on Day 1. Statistical comparisons between Day 5 and Day 1 on C_{max} and AUCs within each TAK-390MR regimen confirmed this observation as well.

After dosing, a similar initial rate of increase in TAK-390 and lansoprazole concentrations was observed. The pharmacokinetics of lansoprazole following oral administration of 15 mg of lansoprazole QD for 1 or 5 days did not appear to be time-dependent.

Safety Results:

Oral doses of 30 mg or 60 mg of TAK-390MR or of 15 mg of lansoprazole administered daily for 5 consecutive days were safe and well tolerated in these healthy subjects. Safety results were similar across the various dosing regimens. No deaths or other serious adverse events occurred, and no subject prematurely discontinued the study because of an adverse event. No consistent, clinically important changes in laboratory test results, vital signs, physical examinations, or ECGs were observed in this study.

Conclusion(s):

A greater increase in intragastric pH was produced by both 30 mg and 60 mg of TAK-390MR, compared to 15 mg of lansoprazole, after a single dose or after 5 consecutive daily doses. The 60-mg dose of TAK-390MR appeared to produce a greater effect on intragastric pH than did the 30-mg dose on Day 1; however, the difference between the 2 doses of TAK-390MR was less pronounced on Day 5.

Dose proportionality was observed for mean C_{max} and AUC values following oral administration of 30 mg or 60 mg of TAK-390MR QD for 1 or 5 days. The exposure of TAK-390MR on Day 5 was generally similar to that on Day 1 following oral administration of 30 mg or 60 mg of TAK-390MR QD.

Oral administration of 30 mg or 60 mg of TAK-390MR once daily for 5 consecutive days was safe and well tolerated in these healthy adult subjects. Safety results were similar across the various dosing regimens.

Study T-P104-100 Plasma gastrin concentration profile

Name of Company: TAP Pharmaceutical Products Inc. Name of Finished Product: TAK-390MR Name of Active Ingredient: R-(+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole				
Title of Study: A Phase 1, Randomized, Open-Label, Crossover, Single-Center Study to Measure Plasma Gastrin Levels Following Administration of 90-mg and 120-mg Oral Doses of a Modified-Release Formulation of TAK-390 and a 30-mg Oral Dose of Lansoprazole in Healthy Subjects				
Investigator (b) (4)				
Study Center (b) (4)				
Publication (reference): None				
Study Period: Date of First Dose: 13 December 2004 Date of Last Procedure: 29 January 2005			Phase of Development: 1	
Objective(s): The objectives of this study were to characterize the plasma gastrin concentration profile on Day 1 and Day 5 following once daily (QD) oral administration of 90 mg or 120 mg of the modified-release formulation of TAK-390 (TAK-390MR) or 30 mg of lansoprazole delayed-release capsules for 5 consecutive days, to evaluate the relationship between the plasma gastrin profile and the pharmacokinetics of 90 mg or 120 mg of TAK-390MR or 30 mg of lansoprazole on Day 1 and Day 5, and to assess the safety of 90 mg and 120 mg of TAK-390MR and 30 mg of lansoprazole following QD oral administration for 5 consecutive days to healthy subjects.				
Methodology: This was a Phase I, randomized, open-label, single-center, multiple-dose, 3-period crossover study. Subjects received a different dosing regimen during each period of the study, so that at study completion each subject had received all 3 regimens. Subjects were randomly assigned to the sequence in which they received each of the 3 different regimens, as summarized in the following table.				
Regimen Sequences				
Sequence	Number of Subjects	Period 1	Period 2	Period 3
1	14	Regimen A	Regimen B	Regimen C
2	14	Regimen B	Regimen C	Regimen A
3	14	Regimen C	Regimen A	Regimen B
Regimen A: 90 mg of TAK-390MR administered QD for 5 consecutive days with 240 mL of water. Regimen B: 120 mg of TAK-390MR administered QD for 5 consecutive days with 240 mL of water. Regimen C: 30 mg of lansoprazole administered QD for 5 consecutive days with 240 mL of water.				
On Day -2 of Period 1 and Day -1 of Periods 2 and 3, subjects were confined to the testing unit, and they remained confined until all study procedures were completed on Day 6 of each period. During each period, dosing began at approximately 0800 hours on Days 1 through 5. A washout interval of at least 14 days separated the last dose of a period from the first dose of the next period. At study completion, a subject was to have received five 90-mg and five 120-mg doses of TAK-390MR and five 30-mg doses of lansoprazole. Safety was monitored through adverse event (AE) reports, concomitant medication usage, 12-lead electrocardiograms (ECGs), physical examinations, vital sign assessments, and laboratory evaluations. The pharmacokinetic and pharmacodynamic profiles of TAK-390MR and of lansoprazole were assessed through blood sampling for pharmacokinetic analysis and determination of plasma gastrin levels for pharmacodynamic analysis. Plasma concentrations of TAK-390 and lansoprazole were determined using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) assay, and plasma gastrin concentrations were determined using a validated sensitive and specific (b) (4) assay. Pharmacokinetic parameters for TAK-390 and lansoprazole in plasma were estimated using standard noncompartmental methods.				

Number of Patients (planned and analyzed): 42 planned and enrolled; 42 subjects were included in the pharmacodynamic analyses, the pharmacokinetic analyses, and the safety analyses.				
Diagnosis and Main Criteria for Inclusion: Male and female subjects between 18 and 55 years of age, inclusive, in general good health.				
Test Product, Dose and Mode of Administration, Batch Number:				
Test Product	Dose	Mode of Administration	Lot Number	Manufacturer
TAK-390MR Capsules	90 mg	Oral	Z540G024	Takeda Pharmaceutical Company Limited
TAK-390MR Capsules	120 mg (as two 60-mg capsules)	Oral	Z540G014	Takeda Pharmaceutical Company Limited
Duration of Treatment: During the 3 crossover periods, each subject was to receive 90 mg and 120 mg of TAK-390MR and 30 mg of lansoprazole QD for 5 consecutive days. The last dose in a period and the first dose in the next period were separated by a washout interval of at least 14 days.				
Reference Therapy, Dose and Mode of Administration, Batch Number:				
Reference Product	Dose	Mode of Administration	Lot Number	Manufacturer
Lansoprazole Capsules	30 mg	Oral	201492E21	Takeda Pharmaceutical Company Limited
Criteria for Evaluation:				
Efficacy: Efficacy was not assessed in this study.				
Pharmacodynamics: Plasma gastrin concentrations were assessed at specified timepoints on Days 1 and 5 of each period. During Periods 1 and 2, fasting plasma gastrin concentrations were also assessed on Days 8 and 12. Plasma samples were analyzed for gastrin concentrations a (b) (4) using a validated assay with a lower limit of quantitation (LLOQ) of 31.00 pg/mL. For statistical analyses, samples with results below the LLOQ were assigned values of 15.5 pg/mL. The area under the curve over a 24-hour dosing interval (AUC ₂₄) was estimated using the linear trapezoidal method.				
Pharmacokinetics: Plasma concentrations of TAK-390 or lansoprazole were determined at designated timepoints on Days 1 and 5 of each period. The analyses of the plasma TAK-390 or lansoprazole concentrations were conducted at (b) (4) using validated LC-MS/MS assay methods. The LLOQ was 5.00 ng/mL. Pharmacokinetic parameters for TAK-390 or lansoprazole in plasma were estimated using standard noncompartmental methods. The pharmacokinetic parameters included the observed maximum concentration (C _{max}); the time to maximum concentration (t _{max}); the terminal-phase rate constant (λ _z); the terminal elimination half-life (t _{1/2z}); the oral clearance (CL/F); the volume of distribution (V _d /F); and the area under the curve (AUC) from zero to time t, (AUC _t , with t being the time corresponding to the last quantifiable concentration), AUC ₂₄ (Day 5 only), and AUC from time zero to infinity (AUC _∞ , Day 1 only).				
Safety: Safety was monitored by assessing AEs, concomitant medication usage, clinical laboratory variables, physical examinations, ECGs, and vital signs.				

Statistical Methods:

Efficacy:

Efficacy was not assessed in this study.

Pharmacodynamics:

Summary statistics (number of subjects in an analysis [N], mean, median, standard deviation [SD], and range) for plasma gastrin concentrations at each timepoint and plasma gastrin AUC₂₄ were generated by regimen for baseline and for Day 1 and Day 5 of each period. The relationship between the plasma gastrin profile and the pharmacokinetics of TAK-390 or lansoprazole were evaluated using a scatter plot of plasma gastrin AUC₂₄ versus TAK-390 or lansoprazole AUC. An analysis of variance (ANOVA) model with factors of sequence, subject within sequence, period, regimen, day, and regimen-by-day interaction was used to evaluate the time required for the fasting gastrin level to return to baseline level following dosing during each regimen. The subject-within-sequence effect was random, while other factors were fixed. A one-way ANOVA model with period effect was used to investigate whether the length of the washout interval between periods was sufficient.

Pharmacokinetics:

For each regimen, TAK-390 or lansoprazole plasma concentration data and pharmacokinetic parameter estimates were tabulated and descriptive statistics computed.

Safety:

All subjects who received at least 1 dose of study drug were included in the analyses of safety.

Treatment-emergent adverse events were summarized for each regimen and overall. Baseline and postdose values and mean change from baseline to postdose were summarized by regimen for clinical laboratory variables and for vital signs. Subjects with laboratory or vital sign results that met the predefined criteria for potentially concerning values were identified.

Summary-Conclusions:

Efficacy Results:

Efficacy was not assessed in this study.

Pharmacodynamic Results:

The mean plasma gastrin concentrations at each timepoint and the mean gastrin AUC₂₄ results at baseline (Day -1 of Period 1) and for each of the 3 regimens are summarized in the following table.

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Gastrin AUC ₂₄ and Concentrations at Baseline and on Days 1 and 5 Following Oral Administration of 90 mg or 120 mg of TAK-390MR or 30 mg of Lansoprazole QD for 5 Days											
Study Day	Measure	AUC ₂₄ (pg·h/mL)	Gastrin Concentration (pg/mL) at Each Specified Timepoint								
			0 hours	2 hours	4 hours	5 hours	9 hours	10 hours	13 hours	14 hours	23.75 hours
Baseline (N = 40)											
Day -1 ^a	Mean	1275.64 ^b	18.2	58.3	33.4	62.2	40.5	74.7	84.6	79.5	NA
	CV%	52 ^b	36	60	59	61	52	75	59	51	NA
90 mg of TAK-390MR (N = 40)											
Day 1	Mean	2548.75	17.7	73.8	89.5	115.2	142.0	148.2	167.8	134.0	52.1
	CV%	64	33	71	75	70	67	87	71	62	87
Day 5	Mean	4156.61	67.6	149.4	197.9	191.4	200.5	236.9	235.7	209.1	83.6
	CV%	60	72	59	65	61	62	81	59	61	80
120 mg of TAK-390MR (N = 40)											
Day 1	Mean	2633.53	20.2 ^a	78.9	100.6	131.5	145.8	142.0	176.7	136.8	49.1
	CV%	56	55 ^b	73	73	75	65	56	57	51	68
Day 5	Mean	4254.78	67.7	160.7	204.6	199.0	202.3	233.1	252.8	204.7	91.4
	CV%	55	79	58	58	61	54	73	55	52	81
30 mg of Lansoprazole (N = 40)											
Day 1	Mean	2442.22	19.0	87.0	106.2	124.6	128.2	133.8	155.6 ^a	130.3	37.2
	CV%	60	47	70	64	67	80	73	56 ^a	56	100
Day 5	Mean	3552.37	42.3	141.7	175.0	168.2	177.4	200.5	209.8	182.5	55.0
	CV%	57	70	56	61	56	66	66	63	56	83

Note: Analysis of all subjects with complete pharmacodynamic data for both Day 1 and Day 5 for all regimens.
h = hour, CV% = percentage of coefficient of variation, NA = not applicable
a Day -1 of Period 1.
b N = 39.
h = hour.

The plasma gastrin 24-hour profiles for all 3 regimens were similar on Day 1. For all 3 regimens, the plasma gastrin 24-hour profiles were higher on Day 5 than on Day 1. However, the gastrin concentrations measured on Day 5 were slightly higher during the 2 TAK-390MR regimens than during the lansoprazole regimen. Higher mean plasma gastrin AUC₂₄ values compared to the baseline gastrin AUC₂₄ value were also observed after administration of the 3 regimens. The mean plasma gastrin AUC₂₄ values for Regimens A, B, and C were comparable on Day 1. For all 3 regimens the mean gastrin AUC₂₄ values were higher on Day 5 than on Day 1. The AUC₂₄ values for 90 mg and 120 mg of TAK-390MR were comparable on Day 5, and both values were slightly higher (17% to 20%) than the corresponding value for 30 mg of lansoprazole. This difference among the gastrin AUC₂₄ values on Day 5 is small compared to the variability observed for the Day 5 results (CV%: 55 to 60).

To investigate how quickly the elevated fasting gastrin concentrations returned to baseline, an ANOVA model with factors of sequence, period, subject within sequence, regimen, day, and regimen-by-day interaction was used to compare the fasting plasma gastrin concentrations on Days 5 (prior to the last dose of each regimen), 6 (23.75 hours after the last dose of each regimen), 8, and 12 to the fasting gastrin level obtained prior to dosing on Day 1 (baseline). This analysis is summarized in the following table.

Mean Fasting Gastrin Concentrations at Baseline and on Days 5, 6, 8, and 12, by Regimen				
Study Day	Measure	Fasting Gastrin Concentration (pg/mL)		
		90-mg TAK-390MR	120-mg TAK-390MR	30-mg Lansoprazole
Baseline ^a	N	41	40	42
	Mean	17.6	20.1	20.3
	SD	5.84	11.07	12.62
5	N	41	41	41
	Mean	67.8***	67.3***	44.8***
	SD	47.91	53.19	33.14
6	N	41	41	41
	Mean	82.6***	91.0***	57.0***
	SD	66.2	72.9	46.7
8 ^b	N	24	26	28
	Mean	36.3**	40.6**	44.7***
	SD	30.41	30.14	52.63
12 ^b	N	25	28	28
	Mean	26.8	28.8	29.6
	SD	18.43	19.63	17.69

a Baseline represents the result obtained just prior to the first dose of each regimen.
b Day 8 and Day 12 samples were collected during Periods 1 and 2 only.
Note: P-values are from the ANOVA model utilizing all available data. Comparisons of the least-square means on Days 5, 8, and 12 to the baseline were performed within each regimen.
*, **, and *** denote p-values of less than 0.05, 0.01, and 0.001, respectively.

The fasting plasma gastrin concentrations at baseline (ie, prior to dosing on Day 1 of each regimen) were similar for 90 or 120 mg of TAK-390MR or 30 mg of lansoprazole. The fasting plasma gastrin level obtained prior to dosing on Day 5 was statistically significantly higher than the corresponding baseline value for all 3 regimens, as was the fasting gastrin level obtained on Day 6, 23.75 hours after the last dose of each regimen. On Day 8 the fasting gastrin levels for all 3 regimens also remained statistically significantly elevated, relative to the corresponding baseline values. By Day 12, seven days after the last dose of study drug, the fasting gastrin levels had returned to near baseline levels; the values for the 3 regimens were comparable and were not statistically significantly different from corresponding baseline values.

The fasting plasma gastrin concentrations obtained prior to dosing on Day 1 of each regimen were not only similar to each other but were also similar to the value obtained at the corresponding timepoint on Day -1 of Period 1, prior to administration of any study drug. This suggests that the 14-day washout interval between consecutive periods was sufficiently long to allow elevated plasma gastrin concentrations to return to baseline levels.

Pharmacokinetic Results:
Mean noncompartmental pharmacokinetic parameter estimates for TAK-390 or lansoprazole for subjects who had complete pharmacokinetic data for both Day 1 and Day 5 for all regimens are summarized in the following table for Regimens A (90-mg TAK-390MR), B (120-mg TAK-390MR), and C (30-mg lansoprazole).

Plasma Pharmacokinetic Parameter Estimates for TAK-390 or Lansoprazole on Days 1 and 5 Following Oral Administration of 90 mg or 120 mg of TAK-390MR or 30 mg of Lansoprazole							
Regimen	Day	Measure	t _{max} (h)	C _{max} (ng/mL)	AUC _t (ng·h/mL)	AUC _{∞ or 24} ^a (ng·h/mL)	t _{1/2z} ^b (h)
A (90 mg of TAK-390MR)	1	N ^c	40	40	40	31	31
		Mean	5.15	1953.90	11223.24	12205.74	1.62
		CV%	43	49	59	58	--
	5	N ^c	40	40	40	31	31
		Mean	5.38	2034.90	11448.75	12540.43	1.71
		CV%	68	48	54	51	--
B (120 mg of TAK-390MR)	1	N ^c	40	40	40	31	31
		Mean	5.38	2725.50	15198.82	16472.62	1.65
		CV%	41	51	56	56	--
	5	N ^c	40	40	40	31	31
		Mean	4.98	2972.50	16573.22	17818.17	1.70
		CV%	42	44	48	47	--
C (30 mg of lansoprazole)	1	N ^c	40	40	40	31	31
		Mean	1.60	850.70	2499.92	2661.53	1.41
		CV%	31	32	50	49	--
	5	N ^c	40	40	40	31	31
		Mean	1.68	892.55	2586.86	2823.47	1.33
		CV%	37	52	50	47	--

a AUC_∞ for Day 1, AUC₂₄ for Day 5.
b Harmonic mean.
c Number of subjects who had complete pharmacokinetic data for the specified variable for both Day 1 and Day 5 for all regimens.
h = hour.

Approximate dose proportionality was observed for mean C_{max} and AUC values following oral administration 90 mg and 120 mg of TAK-390MR. The plasma exposure of TAK-390 on Day 5 was generally similar to that observed on Day 1. The pharmacokinetics of lansoprazole following oral administration of 30 mg of lansoprazole QD for 1 or 5 days were similar to those reported in previous studies of lansoprazole.

The terminal half-lives of TAK-390 following oral administration of either 90 mg or 120 mg of TAK-390MR were similar to that of the lansoprazole delayed-release capsule. The observed variability associated with the pharmacokinetic parameters was similar for all 3 regimens.

The individual plasma gastrin AUC₂₄ versus the TAK-390 or lansoprazole AUC scatter plots showed no apparent relationship between the total plasma gastrin exposure and total plasma exposure of TAK-390 or lansoprazole.

Safety Results:
Oral doses of 90 mg and 120 mg of TAK-390MR and of 30 mg of lansoprazole administered daily for 5 consecutive days were safe and well tolerated in these healthy subjects. Safety results were generally similar across the various dosing regimens. No deaths or other serious adverse events occurred, but 2 subjects prematurely discontinued the study due to AEs, one of which (upper abdominal pain) was considered by the investigator to be probably related to administration of study drug. No consistent, clinically important changes in clinical laboratory test results, vital signs, physical examinations, or ECGs were observed in this study. Notably, the incidence of individual AEs and the magnitude of change in clinical laboratory test results did not consistently increase with the higher dose of TAK-390MR.

Conclusion(s):

Compared to baseline values, administration of 90 mg or 120 mg of TAK-390MR or 30 mg of lansoprazole increased plasma gastrin concentrations, regardless of compound or dose. The increase in plasma gastrin appeared to be greater on Day 5 than on Day 1 during each regimen. After a single dose, the plasma gastrin levels appeared to be comparable for all 3 regimens. After 5 days of dosing, the plasma gastrin levels for the 2 TAK-390MR regimens seemed similar, and both of these gastrin levels seemed slightly higher than the level for the lansoprazole regimen. This difference among the gastrin values on Day 5 is small compared to the variability observed for the Day 5 results. The fasting plasma gastrin concentrations were also increased by multiple doses of TAK-390MR or lansoprazole; these elevated levels slowly decreased after the last dose of study drug during each regimen and returned to near baseline levels by 7 days after the last dose of study drug.

Approximate dose proportionality was observed for mean C_{max} and AUC values following oral administration of 90 mg or 120 mg of TAK-390MR QD for 1 or 5 days. The exposure of TAK-390 on Day 5 was generally similar to that on Day 1 following QD oral administration of 90 mg or 120 mg of TAK-390MR. There was no apparent relationship between the total plasma gastrin exposure and total plasma exposure of TAK-390 or lansoprazole.

Overall, oral administration of 90 mg or 120 mg of TAK-390MR once daily for 5 consecutive days was safe and well tolerated in these healthy adult subjects. Safety results were similar across the various dosing regimens. Notably, the incidence of individual AEs and the magnitude of change in clinical laboratory test results did not consistently increase with the higher dose of TAK-390MR.

Study T-P106-148 Bioavailability/bioequivalence (granules on applesauce versus intact capsule)

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Name of Company: TAP Pharmaceutical Products Inc Name of Finished Product: Dexlansoprazole MR Capsules Name of Active Ingredient: (+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl} sulfinyl]-1H-benzimidazole			
Title of Study: A Phase 1, Open-Label, Two-Way Crossover Study to Assess the Bioavailability of Dexlansoprazole MR 90 mg When the Capsule Contents Are Administered Sprinkled Over Applesauce Relative to a Single, Oral Dose of Dexlansoprazole MR 90 mg Intact Capsule Administered Orally			
Investigator: 1 investigator			
Study Center: Single investigative site in the United States of America			
Publication (Reference): None			
Study Period: Date of First Dose: 30 October 2006 Date of Last Procedure: 05 December 2006		Phase of Development: 1	
Objective: The objective of this study was to evaluate the relative bioavailability and assess the bioequivalence of dexlansoprazole (TAK-390) following administration of a single, oral dose of 90 mg of dexlansoprazole modified release (MR [TAK-390MR]) as granules sprinkled over 1 tablespoon of applesauce relative to administration of a single, oral dose of 90 mg of dexlansoprazole MR as an intact capsule.			
Methodology: This was a Phase 1, single-center, open-label, randomized, two-period crossover study. Healthy male and female subjects received a different dosing regimen during each period of the study. Sixty subjects were randomly assigned to 2 sequence groups, which determined the sequence in which they received each of the 2 different regimens, as summarized in the following table.			
Regimen Sequences			
Sequence Group	Number of Subjects	Period 1	Period 2
1	30	Regimen A	Regimen B
2	30	Regimen B	Regimen A
Regimen A: Granules from a single capsule of 90 mg of dexlansoprazole MR administered orally sprinkled over 1 tablespoon of applesauce. Regimen B: A single, intact capsule of 90 mg of dexlansoprazole MR administered orally.			
On Day -1 of each period, subjects were confined to the clinical testing facility, and they remained confined until all study procedures were completed on Day 2 of each period. Subjects received a single, oral dose of 90 mg of dexlansoprazole MR on Day 1 of each period, according to the sequence group to which they had been assigned. Dosing began at approximately 0900 hours on Day 1 following at least a 10-hour fast, and subjects remained fasting for 4 hours after dosing, when lunch was served. A washout interval of at least 5 days separated the dose of Period 1 from the dose of Period 2. Sequential blood samples for determination of dexlansoprazole plasma concentrations were drawn on Day 1 of each period, starting prior to dose and continuing through 24 hours after dosing, and pharmacokinetic parameters were estimated.			
Number of Subjects (Planned and Analyzed): Sixty subjects were planned and enrolled. Fifty subjects were included in the statistical analyses of the dexlansoprazole pharmacokinetic parameters, and descriptive statistics were provided for dexlansoprazole pharmacokinetic parameters for 50 subjects with valid estimates for both regimens. All 60 subjects were included in the safety analyses.			
Diagnosis and Main Criteria for Inclusion: Male and female subjects between 18 and 55 years of age, inclusive, and in general good health.			

Duration of Treatment: Over the 2 crossover periods, each subject was to have received a single, oral dose of 90 mg of dexlansoprazole MR administered as granules from a single capsule sprinkled over 1 tablespoon of applesauce (Regimen A) and a single, oral dose of 90 mg of dexlansoprazole MR administered as an intact capsule (Regimen B).

Test Product, Dose and Mode of Administration, and Lot Numbers:

Test Product	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Drug Product Lot Number
Dexlansoprazole MR	One 90-mg Capsule ^a	90 mg on Day 1 of each period ^a	Oral ^a	Takeda Pharmaceutical Company Limited	Z540S051

a For Regimen A, the granules from a single capsule were administered sprinkled over 1 tablespoon of applesauce. For Regimen B, a single, intact capsule was administered orally.

Reference Therapy, Dose and Mode of Administration, and Lot Numbers:

No reference therapy was utilized for this study.

Criteria for Evaluation:

Pharmacokinetics:

Dexlansoprazole plasma concentrations were determined using a validated liquid chromatography tandem mass spectrometry assay with a lower limit of quantitation of 5.00 ng/mL. Pharmacokinetic parameters for dexlansoprazole in plasma were estimated using standard noncompartmental methods. The pharmacokinetic parameters included: the maximum (peak) plasma drug concentration (C_{max}), the time to maximum (peak) drug concentration (t_{max}), the apparent terminal elimination rate constant (λ_z), the apparent terminal elimination-phase half-life ($t_{1/2z}$), area under the plasma concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_t) and to infinity (AUC_{∞}). In addition, the oral clearance (CL/F) and the apparent volume of distribution during the terminal phase (V_z/F) were estimated.

Safety:

Safety was monitored by assessing adverse events (AEs), concomitant medication usage, clinical laboratory variables, electrocardiograms (ECGs), physical examinations, and vital signs.

Statistical Methods:

Pharmacokinetics:

Descriptive statistics for the plasma concentrations and for each of the pharmacokinetic parameters for dexlansoprazole were computed for each regimen. To evaluate the relative bioavailability and assess the bioequivalence of dexlansoprazole following administration of the 2 dosing regimens, analyses of variance (ANOVAs) were performed on dexlansoprazole t_{max} and the natural logarithms of C_{max} , AUC_t , and AUC_{∞} using a model with factors of sequence, subjects nested within sequence, period, and regimen. The factor of subjects-within-sequence was treated as random, and all other factors were fixed. Within the framework of the ANOVA model, the relative bioavailability of dexlansoprazole was assessed by point estimates and 90% confidence intervals for the ratios of central values of C_{max} , AUC_t , and AUC_{∞} from a single, oral dose of 90 mg of dexlansoprazole MR administered as granules from a single capsule sprinkled over 1 tablespoon of applesauce (Regimen A) to corresponding values from the same dose administered as an intact capsule (Regimen B). The 90% confidence interval was obtained by exponentiating the lower and upper bound of the 90% confidence interval for the difference in the least square means of natural logarithms of C_{max} and AUCs. A conclusion of bioequivalence between the 2 regimens was made with respect to C_{max} , AUC_t , and AUC_{∞} if the 90% confidence intervals were completely contained within the equivalence range of 0.80 and 1.25.

Safety:

All subjects who received at least 1 dose of study drug were included in the analyses of safety.

Treatment-emergent AEs were summarized for each regimen and overall. Baseline and postdose values and mean change from baseline to postdose were summarized across regimens for clinical laboratory variables and by regimen for vital signs.

Summary and Conclusions:**Baseline Demographics:**

Forty-eight (80%) subjects were male, and 12 (20%) were female. Thirty-six (60%) subjects were black, 20 (33%) were white, and 4 (7%) were American Indian/Alaskan native, Asian, or multiracial. Thirteen (22%) subjects were Hispanic or Latino. The mean age of the subjects was 31.3 years (standard deviation: 8.27 years).

Pharmacokinetic Results:

Noncompartmental pharmacokinetic parameter estimates for dexlansoprazole following administration of a single, oral dose of 90 mg of dexlansoprazole MR as either granules from a single capsule sprinkled over 1 tablespoon of applesauce (Regimen A) or as a single, intact capsule (Regimen B) are summarized below:

Summary of Pharmacokinetic Parameter Estimates for Dexlansoprazole Following a Single, Oral Dose of 90 mg of Dexlansoprazole MR During Each Regimen

Regimen	Measure	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_{∞} (ng·h/mL)	λ_z (h ⁻¹)	$t_{1/2}^a$ (h)	CL/F (L/h)	V_z/F (L)
A	N	50	50	50	49	49	49	49	49
	Mean	4.71	1840.76	10127.04	10416.48	0.43	2.08 (1.62)	12.92	32.16
	%CV	48	54	68	71	48	57	62	48
B	N	50	50	50	49	49	49	49	49
	Mean	4.73	1966.78	10736.08	11093.38	0.43	2.14 (1.63)	12.14	31.20
	%CV	44	56	72	75	47	60	62	58

Note: Regimen A = Granules from a single capsule of 90 mg of dexlansoprazole MR administered orally sprinkled over 1 tablespoon of applesauce. Regimen B = A single, intact capsule of 90 mg of dexlansoprazole MR administered orally.

h = hour; N = total number of subjects in analyses; %CV = percent coefficient of variation

a Arithmetic mean (harmonic mean).

Following administration of a single, oral dose of 90 mg of dexlansoprazole MR as granules sprinkled over 1 tablespoon of applesauce (Regimen A) or as a single, intact capsule (Regimen B), the mean plasma concentration-time curves were nearly superimposable. The mean pharmacokinetic parameter estimates obtained after Regimen A were similar to those obtained after Regimen B.

The statistical assessment of the relative bioavailability and bioequivalence of dexlansoprazole following administration of Regimen A and Regimen B was performed via 90% confidence intervals for the ratios of the central values for C_{max} , AUC_t , and AUC_{∞} . The results of this assessment are presented in the following table.

Statistical Assessment of the Relative Bioavailability and Bioequivalence of Dexlansoprazole Following Administration of Regimen A and Regimen B

Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
Regimen A versus Regimen B		
C_{max}	0.94	(0.8695 - 1.0225)
AUC_t	0.95	(0.8943 - 0.9998)
AUC_{∞}	0.94	(0.8898 - 0.9951)

Note: Regimen A = Granules from a single capsule of 90 mg of dexlansoprazole MR administered orally sprinkled over 1 tablespoon of applesauce. Regimen B = A single, intact capsule of 90 mg of dexlansoprazole MR administered orally.

The 90% confidence intervals for the ratio of the central values of dexlansoprazole C_{max} , AUC_t , and AUC_{∞} obtained for Regimen A and Regimen B were within the bioequivalency range of 0.80 to 1.25.

Summary and Conclusions (Continued):**Safety Results:**

No clinically important difference in safety results was observed between the 2 dexlansoprazole MR dosing regimens in this study. Nine subjects (15%) experienced at least 1 treatment-emergent AE during their participation in the study. The number (%) of subjects experiencing at least 1 AE during a given dosing regimen was 4 (7%) during Regimen A (90 mg of dexlansoprazole MR as granules sprinkled over 1 tablespoon of applesauce) and 5 (9%) during Regimen B (90 mg of dexlansoprazole MR as an intact capsule). The only Medical Dictionary for Regulatory Activities (MedDRA) High Level Terms (HLTs) experienced by ≥ 2 subjects during either regimen or across regimens were Nausea and Vomiting Symptoms (1 subject during Regimen A and 2 subjects during Regimen B) and Urinary Abnormalities (1 subject during Regimen A and 1 subject during Regimen B). One subject (2%) experienced 1 treatment-emergent MedDRA HLT that was considered by the investigator to be possibly related to administration of study drug; this subject experienced related Nausea and Vomiting Symptoms (MedDRA HLT) during Regimen B. No deaths or other serious adverse events occurred, but 2 subjects prematurely discontinued from the study due to an AE. Subject 155 experienced Vomiting on Study Day 5 (during the washout interval after receiving Regimen A on Day 1 of Period 1) and Ketonuria and Hypokalemia on Study Day 6 (Day -1 of Period 2) and was prematurely discontinued from the study. Subject 156 experienced White Blood Cell Count Increased on Study Day 6 (Day -1 of Period 2, after receiving Regimen B on Day 1 of Period 1) and was prematurely discontinued from the study. These AEs were considered by the investigator to be not related to administration of study drug.

No consistent, clinically important changes in laboratory test results, vital signs, ECGs, or physical examinations were observed.

Conclusions:

The alternative oral delivery option of administration of a single dose of 90 mg of dexlansoprazole MR as granules from a single capsule sprinkled over 1 tablespoon of applesauce was bioequivalent, measured by C_{max} , AUC_0-12 , and $AUC_{0-\infty}$, to administration of the same dose as a single, intact capsule.

In this study, no safety concerns were associated with the administration to healthy subjects of 2 doses of dexlansoprazole MR, 1 dose administered as granules from a single capsule sprinkled over 1 tablespoon of applesauce and 1 dose administered as an intact capsule.

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Study M01-309 (may not be needed)

Name of Company: TAP Pharmaceutical Products Inc.		Individual Study Table Referring to Item of the Submission: N/A		
Name of Finished Product: N/A		Volume: N/A		
Name of the Active Ingredient: N/A		Page: N/A		
Title of Study: A Phase 1, Randomized, Open-Label, Multiple Dose, Crossover, Single-Center Study to Compare the Pharmacodynamics, Pharmacokinetics, and Safety of Two Dose Levels of TAK-390 (R+ Enantiomer of Lansoprazole) and One Dose Level of T-168391 (S- Enantiomer of Lansoprazole) with Reference Lansoprazole in Healthy Subjects				
Investigator(b) (4)				
Study Center: (b) (4)				
Publication (reference): None				
Study Period (years): Approximately 4 months			Phase of Development: 1	
Date First Subject Dosed: 21 August 2001				
Date Last Subject Completed Dosing: 07 October 2001				
Objectives: The primary objective of this study was to compare the pharmacodynamics of the R+ enantiomer and S- enantiomer of lansoprazole to racemate lansoprazole. The secondary objectives of this study were to compare the pharmacokinetic profiles of the test R+ enantiomer and S- enantiomer, when dosed separately, to the reference racemate lansoprazole and to summarize the safety profile for each study medication.				
Methodology: This was a Phase 1, randomized, open-label, 4-way crossover study to compare 20 mg and 30 mg doses of TAK-390 (R+ enantiomer) and a 30 mg dose of T-168391 (S- enantiomer) to 30 mg lansoprazole (racemate). Thirty-six healthy male and female subjects were enrolled at a single study center.				
Subjects who completed the screening procedures and were eligible to enter the study were randomly assigned in equal numbers to 1 of 4 regimen sequences. The sequences were such that each subject received all 4 regimens.				
Sequence	Period 1	Period 2	Period 3	Period 4
1	A	C	B	D
2	B	A	D	C
3	C	D	A	B
4	D	B	C	A
A=TAK-390 (R+ enantiomer) 30 mg PO for 5 consecutive days of dosing B= TAK-390 (R+ enantiomer) 20 mg PO for 5 consecutive days of dosing C=T-168391 (S- enantiomer) 30 mg PO for 5 consecutive days of dosing D=Lansoprazole (racemate) 30 mg PO for 5 consecutive days of dosing				
Each subject completed all screening procedures within 2 weeks prior to the initial dosing day. During each crossover period, subjects were confined for approximately 5 ½ days. For each regimen, study drug was administered for 5 consecutive days. A washout interval of at least 7 days separated the last dose of a period from the first dose of any subsequent period. Gastric pH was measured over 24-hour intervals on Days 1 and 5 of each crossover period. Plasma drug concentrations were obtained on Days 1 and 5 of each crossover period. The safety of study medications was monitored through physical examinations including vital signs, laboratory evaluations, electrocardiograms, as well as adverse event and concurrent medication assessments.				

Number of Subjects (Planned and Analyzed): 36 subjects planned for enrollment; 37 subjects were dosed (1 of these was a replacement subject).

Each dosing regimen	R+ Enantiomer 30 mg	R+ Enantiomer 20 mg	S- Enantiomer 30 mg	Lansoprazole 30 mg
Number of subjects planned	36	36	36	36
Number of subjects dosed	35	35	34	33

Diagnosis and Main Criteria for Inclusion:

Male and (non-pregnant) female adults, 18 - 45 years of age, inclusive, in generally good health.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Test Product	Dose	Mode of Administration	Finishing Lot Number (Manufacturer's Lot Number)
TAK-390	30 mg (2x15 mg capsules)	Oral	Z5274012
TAK-390	20 mg (1x20 mg capsule)	Oral	Z5275012
T-168391	30 mg (2x15 mg capsules)	Oral	Z5331011

Reference Therapy, Dose and Mode of Administration, and Lot Number:

Reference Product	Dose	Mode of Administration	Finishing Lot Number (Manufacturer's Lot Number)
Lansoprazole	30 mg (1x30 mg capsule)	Oral	62-017-4R

Duration of Dosing: Five consecutive days during each of the 4 crossover periods.

Criteria for Evaluation:

Pharmacokinetics The R+ enantiomer, the S- enantiomer, and lansoprazole (racemate) pharmacokinetic parameters estimated for Days 1 and Days 5 of each crossover period included the maximum observed concentration (C_{max}), the time elapsed to C_{max} (t_{max}), the area under the plasma concentration-time curve from time zero to infinite time (AUC_{∞}), the terminal elimination rate constant (λ_z), and the elimination half-life ($t_{1/2}$).

Pharmacodynamics Pharmacodynamic variables included mean gastric pH over the entire 24-hour period, as well as over each of the following post-dosing intervals: 0-5 hours, >5-10 hours, >10-15 hours, and >15-24 hours. In addition, the percentage of time that gastric pH was greater than 3, 4, 5, and 6 for the 24-hour monitoring period were also analyzed.

Safety The safety of the study medications was monitored through physical examinations including vital signs, laboratory evaluations, electrocardiograms, as well as adverse event and concurrent medication assessments.

Statistical Methods: Descriptive statistics for the plasma concentration data and derived plasma pharmacokinetic parameters for R+ enantiomer and S- enantiomer were computed for all subjects. Missing values and not determinable data were excluded from the calculation of the summary statistics. For each enantiomer and day, the pharmacokinetic parameters of the 4 regimens were compared using an ANOVA model with effects for sequence, subject nested within sequence, period and regimen. The analysis of C_{max} and AUC was performed on natural logarithmic transformed data.

For Day 1 and 5 of each crossover period, the gastric pH of the 4 regimens were compared with a crossover analysis of variance (ANOVA) model that included effects for sequence, subject nested within sequence, regimen and period. Analyses were performed on the mean gastric pH during the 24-hour monitoring period, as well as over the following time intervals relative to the beginning of dosing: 0-5 hours, >5-10 hours, >10-15 hours, and >15-24 hours. For Day 1 and 5 of each crossover period, point estimates and 95% confidence intervals were determined for the differences of the mean pH between 30 mg TAK-390 and 30 mg lansoprazole, 20 mg TAK-390 and 30 mg lansoprazole, and 30 mg T-168391 and 30 mg lansoprazole. In addition, the percentage of time that pH exceeded 3, 4, 5, and 6 during the 24-hour monitoring period were also analyzed.

The number and percentage of subjects having adverse events were tabulated by COSTART V term and body system for each regimen. Laboratory values outside the normal reference range were summarized and noted if clinically significant.

Summary/Conclusions:

Pharmacokinetic Results Following administration of lansoprazole 30 mg for 1 or 5 days, R+ lansoprazole accounted for 85% of the total lansoprazole C_{max} compared to S- lansoprazole. R+ lansoprazole also accounted for approximately 90% of the total AUC_{∞} compared to S- lansoprazole. Based on these results, it would be expected that the plasma exposure from a 30 mg dose of TAK-390 would be approximately twice that of a 30 mg dose of lansoprazole.

After administration of TAK-390 30 mg for 1 or 5 days, R+ lansoprazole mean C_{max} and AUC_{∞} were approximately 90% and 50% greater, respectively, than the lansoprazole mean C_{max} and AUC_{∞} from a lansoprazole 30 mg dose. The t_{max} and half-life of R+ lansoprazole were also similar to those values found for lansoprazole after administration of lansoprazole 30 mg. In contrast, after administration of TAK-390 20 mg, R+ lansoprazole C_{max} and AUC_{∞} , as well as half-life and t_{max} , were similar to the corresponding lansoprazole values. S- lansoprazole was not detected after administration of TAK-390 20 or 30 mg. Collectively, the results from the TAK-390 dosing regimens indicate that the plasma levels drug rise with an increase in TAK-390 dose from 20 mg to 30 mg.

Administration of T-168391 30 mg for 1 or 5 days resulted in much lower plasma levels than any other regimen. Most of the plasma exposure was comprised of S- lansoprazole, although R+ lansoprazole was detected in measurable quantities in the plasma of some subjects, confirming the *in vivo* interconversion of S- lansoprazole to R+ lansoprazole.

Pharmacodynamic Results The mean gastric pH-time profiles following the administration of each regimen suggested that:

- 20 mg and 30 mg TAK-390 provided similar or greater pH to 30 mg lansoprazole.
- Although the total plasma exposure of lansoprazole (as indicated by AUC) from 30 mg TAK-390 was higher than that of 20 mg TAK-390 and 30 mg lansoprazole, no comparable increasing effect on the gastric pH with the higher plasma levels was observed.
- Oral administration of 30 mg T-168391 provided much lower lansoprazole plasma exposure and was less pharmacologically effective than 30 mg lansoprazole on both Day 1 and Day 5.
- The mean gastric pH of all regimens increased after 5-day administration relative to the corresponding mean gastric pH values on Day 1.

A summary of the mean gastric pH values based on 15-minute medians over the entire 24 hours as well as over several time intervals relative to the beginning of dosing on Days 1 and 5 is presented below.

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Mean Gastric pH Measurements on Days 1 and 5				
Mean Gastric pH	Regimen			
	TAK-390 20 mg	TAK-390 30 mg	T-168391 30 mg	Lansoprazole 30 mg
Day 1				
Entire 24 hours	3.11	3.58*	2.70***	3.32
0-5 Hours	3.04	3.47**	2.54	2.89
>5-10 Hours	3.63**	4.23	3.27***	4.06
>10-15 Hours	3.37*	4.01	2.83***	3.72
>15-24 Hours	2.71	3.03	2.34***	2.93
Day 5				
Entire 24 hours	4.14	4.34	3.40***	4.17
0-5 Hours	4.61	5.09*	3.70**	4.48
>5-10 Hours	4.42	4.70	3.78***	4.59
>10-15 Hours	3.93	4.13	3.33***	4.09
>15-24 Hours	3.83	3.83	3.05***	3.81
* ** *** Indicates statistical significance from 30 mg lansoprazole at 0.05, 0.01, or 0.001 level, respectively. Cross-reference: Drug Metabolism Report, Appendix 16.5.				
A summary of the mean 24-hour gastric pH and the mean percentage of time, based on 15-minute intervals, that the mean gastric pH values remained above 3, 4, 5 and 6 during the entire 24-hour monitoring period on Days 1 and 5 is presented below:				
Mean 24-Hour Gastric pH and Mean Percentage of Time that 24-Hour Gastric pH Values Were Above 3, 4, 5, and 6 on Days 1 and 5				
Pharmacodynamic Parameters	Regimen			
	TAK-390 20 mg	TAK-390 30 mg	T-168391 30 mg	Lansoprazole 30 mg
Day 1				
Mean 24-hour pH	3.11	3.58*	2.70***	3.32
% of time pH ≥ 3	36.37*	45.56	27.01***	42.16
% of time pH ≥ 4	27.53*	37.11	19.55***	33.80
% of time pH ≥ 5	19.98	28.04	13.93***	23.50
% of time pH ≥ 6	11.66	17.86**	8.81	12.37
Day 5				
Mean 24-hour pH	4.14	4.34	3.40***	4.17
% of time pH ≥ 3	58.33	62.97	41.51***	59.60
% of time pH ≥ 4	48.18	52.90	33.11***	49.94
% of time pH ≥ 5	37.27	40.17	23.70***	37.37
% of time pH ≥ 6	25.07	28.78	16.10***	24.47
* ** *** Indicates statistical significance from 30 mg lansoprazole at 0.05, 0.01, or 0.001 levels, respectively. Cross-reference: Drug Metabolism Report, Appendix 16.5.				
Safety Results Overall, 62% of the subjects experienced at least 1 adverse event during the study. The most frequently experienced treatment-emergent adverse event was accidental injury (38%), followed by headache (8%), pharyngitis (8%), vomiting (8%), syncope (5%) and rhinitis (5%). Each of the accidental injury events was throat soreness/nasal pain or discomfort associated with placement of the pH probe. All adverse events reported during the dosing periods were considered mild or moderate in intensity.				

Similar proportions (23% to 26%) of subjects experienced adverse events in each of the 4 dosing regimens. No remarkable differences were noted among the dosing regimens for the incidence of any specific adverse event.

No subject died, experienced a serious adverse event, or prematurely discontinued due to an adverse event throughout the course of the study.

Sporadic changes in laboratory and vital signs values were identified; however, none was considered clinically significant. No clinically significant changes in ECGs were observed.

Conclusions Following administration of lansoprazole 30 mg (racemate) for 1 or 5 days, the R+ enantiomer comprised 85% of the total lansoprazole C_{max} and 90% of the total $AUC_{0-\infty}$, versus the S- enantiomer.

Administration of TAK-390 at the 20 mg dose achieved C_{max} and $AUC_{0-\infty}$ results comparable to lansoprazole 30 mg. At the 30 mg dose, the TAK-390 results were even 90% and 50% greater. Conversely, the plasma levels for T-168391 were much lower.

All regimens increased mean intragastric pH, and were more effective after 5 days of repeated administration than 1 day of single administration. Both 20 mg and 30 mg TAK-390 also outperformed 30 mg lansoprazole, but the pharmacological effect of TAK-390 30 mg failed to match its plasma elevation. Administration of T-168391 produced the least effect on intragastric pH.

Safety results indicated that similar proportions of subjects experienced adverse events in each of the 4 dosing regimens. No subject experienced a serious adverse event or prematurely discontinued due to an adverse event throughout the course of the study. None of the changes in laboratory, ECG, and vital sign values were considered clinically significant. In conclusion, administration of lansoprazole and its enantiomers was well tolerated by study subjects.

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Study Number T-P105-115 Hepatic impairment

Name of Company: TAP Pharmaceutical Products Inc					
Name of Finished Product: Dexlansoprazole MR Capsules					
Name of Active Ingredient: (+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl} sulfinyl]-1H-benzimidazole					
Title of Study: A Phase 1, Open-Label, Parallel Study to Evaluate the Pharmacokinetics and Safety of a Single Oral Dose of Dexlansoprazole MR (60 mg) in Subjects With Normal or Moderately Impaired Hepatic Function					
Investigators: 4 investigators					
Study Centers: 4 sites, all in the United States					
Publication (Reference): None					
Study Period:			Phase of Development: 1		
Date of First Dose: 22 December 2005					
Date of Last Procedure: 08 November 2006					
Objectives:					
<ul style="list-style-type: none"> To evaluate the pharmacokinetics of a single oral dose of dexlansoprazole MR (TAK-390MR, 60 mg) when administered to subjects with moderate hepatic impairment and subjects with normal hepatic function. To evaluate the safety of a single oral dose of dexlansoprazole MR (60 mg) when administered to subjects with moderate hepatic impairment and subjects with normal hepatic function. 					
Methodology: This was a Phase 1, open-label, parallel-group, single-dose study. Twelve subjects with normal hepatic function and 12 subjects with moderate hepatic impairment received a single 60 mg oral dose of dexlansoprazole MR. The subjects with moderate hepatic impairment were enrolled as they became available, based on Child-Pugh classification (Child-Pugh B). Subjects with normal hepatic function were matched to subjects with hepatic impairment with respect to gender, weight at the Screening Visit (± 10 kg), age (± 4 years), and smoking status (smoker or nonsmoker). Following administration of dexlansoprazole MR, blood samples were drawn at various timepoints for plasma concentration determinations of dexlansoprazole, 5-hydroxy dexlansoprazole, and dexlansoprazole sulfone using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay method. The values for the lower limit of quantitation (LLOQ) of dexlansoprazole, 5-hydroxy dexlansoprazole, and dexlansoprazole sulfone assay were 10.0, 1.00, and 2.00 ng/mL, respectively.					
The in vitro protein binding of [14 C]dexlansoprazole at a nominal concentration of 5 μ g/mL was determined using ultrafiltration in predose plasma samples obtained from each subject.					
Number of Subjects (Planned and Analyzed): 16 plus up to 8 additional (8 plus up to 4 additional with moderate hepatic impairment, and 8 plus up to 4 additional with normal hepatic function) planned, 24 enrolled, and 24 were analyzed.					
Diagnosis and Main Criteria for Inclusion: Male and female subjects between 18 and 65 years of age, with moderate chronic hepatic impairment or normal hepatic function					
Duration of Treatment: Subjects received a single dose of dexlansoprazole MR 60 mg capsule.					
Test Product, Dose and Mode of Administration, and Lot Number:					
Test Product	Drug Product Strength	Study Dose	Mode of Administration	Manufacturer	Lot Number
Dexlansoprazole MR	60 mg Capsule	60 mg	Oral	Takeda Pharmaceutical Co Ltd	Z540R011
Reference Therapy, Dose and Mode of Administration, and Lot Number: Not applicable.					

Criteria for Evaluation:**Pharmacokinetics:**

Pharmacokinetic (PK) parameters for dexlansoprazole, 5-hydroxy dexlansoprazole, and dexlansoprazole sulfone in plasma were estimated using standard noncompartmental methods. For dexlansoprazole, the PK parameters included: the maximum (peak) plasma concentration (C_{max}), the time to maximum (peak) drug concentration (t_{max}), the apparent terminal elimination-rate constant (λ_z), the apparent terminal elimination-phase half life ($t_{1/2}$), area under the plasma concentration-time curve (AUC) from time zero to the time of last measurable concentration (AUC_t), AUC from time zero to infinity (AUC_{∞}), the oral clearance (CL/F), apparent volume of distribution during the terminal phase (V_z/F), unbound maximum (peak) plasma concentration ($C_{max,u}$), unbound AUC from time zero to infinity ($AUC_{\infty,u}$), and unbound oral clearance (CL_u/F). For 5-hydroxy dexlansoprazole and dexlansoprazole sulfone, the pharmacokinetic parameters estimated were t_{max} , C_{max} , AUC_t , and metabolite to parent drug AUC_t ratio.

Safety:

Safety was evaluated by monitoring adverse events (AEs) and assessing physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory test results.

Statistical Methods:**Pharmacokinetics:**

For each analyte (dexlansoprazole, 5-hydroxy dexlansoprazole, and dexlansoprazole sulfone), plasma concentration data and PK parameters were tabulated and descriptive statistics computed by subject groups and overall.

An assessment of the relationship of hepatic function and pharmacokinetic parameters was performed via an analysis of variance (ANOVA). For dexlansoprazole t_{max} , λ_z , and natural logarithms of C_{max} , AUC_t , AUC_{∞} , $C_{max,u}$, and $AUC_{\infty,u}$ were analyzed; for metabolites (ie, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone), t_{max} , natural logarithms of C_{max} , AUC_t and AUC_{∞} , as well as the metabolite-to-parent ratios for AUC_t were analyzed. The metabolite-to-parent ratios for AUC_t were natural logarithm-transformed in the ANOVA models as well. The ANOVA model included hepatic function group as a factor. The effect of site was also tested within the ANOVA model frame work with site as an additional factor. If the effect of site was not statistically significant ($p > 0.05$), it was not included in the final ANOVA model.

Safety:

Adverse events that started after the Day 1 dosing or worsened in severity after the Day 1 dosing were summarized by subject group and overall. AEs were classified according to Medical Dictionary of Regulatory Activities (MedDRA) System Organ Class (SOC), High Level Term (HLT), and Preferred Term (PT), and were tabulated with a breakdown by subject group and by event severity. Similar AE tabulations were performed on those events assessed by the investigator as related (possibly or definitely) to study drug. A subject with 1 or more adverse events within the same level of the MedDRA term was counted only once in that level using the most extreme incident (most severe for the severity tables and most related for the relationship to study drug tables).

Clinical laboratory variables were summarized for each subject group utilizing descriptive statistics (N, mean, median, SD, and range) for baseline, postdosing, and change from baseline to postdose values. The baseline value was the last measurement obtained prior to the Day 1 dosing. Postdosing laboratory values were the values collected on Day 2. Only laboratory values collected the day after the Day 1 dosing were included in the analyses. No statistical tests were performed.

Vital signs (systolic blood pressure, diastolic blood pressure, temperature, and pulse rate) were summarized for each subject group utilizing descriptive statistics (N, mean, median, SD, and range) for baseline, Day 1, postdose (Day 2), and change from baseline to postdose values. The baseline value was defined as the last measurement obtained prior to the Day 1 dosing. If more than 1 vital sign parameter value was measured on the same day postdose, the latest value was used. Only vital signs collected within 1 day after the Day 1 dosing were included in the analyses. No statistical tests were performed.

Statistical Methods:**Safety (Cont):**

The number and percentage of subjects meeting sponsor-defined potentially clinically important (PCI) criteria was also summarized for clinical laboratory tests and vital signs.

Electrocardiogram comments were coded by the sponsor using the MedDRA coding dictionary. The number and percentage of subjects with treatment-emergent findings were summarized.

Summary and Conclusions:**Demographics:**

Gender: Male 12 (50%) and Female 12 (50%); Race: Black 4 (17%) and White (20, 83%); Ethnicity: 13 Hispanic or Latino and 11 Not Hispanic or Latino; Age: 50.9 ± 6.09 (range 36 - 63) years; Weight: 85.7 ± 13.61 (range 54 - 111) kg; Height: 169.1 ± 8.53 (range 154 - 184) cm.

Pharmacokinetics Results:

Noncompartmental pharmacokinetic parameter estimates for dexlansoprazole in subjects with normal hepatic function and subjects with moderate hepatic impairment following a single 60 mg oral dose of dexlansoprazole MR are summarized below:

Hepatic Function Group		t_{max} (h)	C_{max} (ng/mL)	$C_{max,u}$ (ng/mL)	AUC_m (ng·h/mL)	$AUC_{m,u}$ (ng·h/mL)	CL/F (L/h)	CL ₀ /F (L/h)	$t_{1/2}$ ^b (h)
Dexlansoprazole									
Normal Function ^a	Mean	4.67	912.25	17.91	7562.63	149.98	16.57	835.62	2.66 (1.56)
	CV(%)	55	54	51	130	129	56	55	116
Moderate Impairment ^a	Mean	4.92	1314.50	27.28	16306.06	350.65	5.65	281.91	7.12 (4.36)
	CV(%)	63	51	45	56	59	77	86	71

^a N = 12.

^b Arithmetic mean (harmonic mean).

Following a single 60 mg oral dose of dexlansoprazole MR, the rate of systemic absorption of dexlansoprazole, as measured by t_{max} and C_{max} , was not statistically significantly different between subjects with moderate hepatic impairment and normal hepatic function; however, mean total and unbound C_{max} values were approximately 1.5-times greater in the hepatically impaired subjects compared to subjects with normal hepatic function. In contrast, the extent of dexlansoprazole absorption (AUC) was higher in subjects with moderate hepatic impairment when matched to subjects with normal hepatic function by gender, age, weight and smoking status. Mean plasma exposures (AUCs) of total and unbound dexlansoprazole for subjects with moderate hepatic impairment were approximately 2-times higher and statistically significantly different compared to subjects with normal hepatic function. This was reflected in an approximately 66% decrease in CL/F and a 3-fold increase in the harmonic mean $t_{1/2}$ of dexlansoprazole in subjects with moderate hepatic impairment compared to those with normal hepatic function.

In vitro mean protein binding of [¹⁴C]dexlansoprazole at a nominal concentration of 5 µg/mL in plasma was similar between subjects with moderately impaired hepatic function (1.99 ± 0.16) compared to those subjects with normal hepatic function (2.13 ± 0.40).

A summary of the mean PK parameter estimates for 5-hydroxy dexlansoprazole and dexlansoprazole sulfone in normal and hepatically impaired subjects following a single 60 mg oral dose of dexlansoprazole MR follows.

Hepatic Function Group		t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_t^b Ratio
5-Hydroxy Dexlansoprazole					
Normal Function ^a	Mean (CV[%])	4.54 (68)	36.30 (55)	189.92 (57)	0.05 (51)
Moderate Impairment ^a	Mean (CV[%])	5.00 (62)	10.09 (89)	77.30 (58)	0.01 (106)
Dexlansoprazole Sulfone					
Normal Function ^a	Mean (CV[%])	4.00 (103)	11.40 (118)	96.15 (241)	0.01 (138)
Moderate Impairment ^a	Mean (CV[%])	8.63 (51)	54.60 (118)	840.52 (115)	0.05 (81)

^a N = 12.

^b Metabolite AUC_t to dexlansoprazole AUC_t ratio.

The disposition kinetics of the 2 major circulating inactive metabolites of dexlansoprazole were altered in subjects with impaired hepatic function compared to those subjects with normal hepatic function. The plasma exposure of the 2 metabolites was minor compared to dexlansoprazole, as the mean AUC_t values for the metabolites were $\leq 5\%$ of that for dexlansoprazole. Administration of a single 60 mg dose of dexlansoprazole MR to subjects with moderate hepatic impairment resulted in a statistically significantly different and lower mean 5-hydroxy dexlansoprazole C_{max} and AUC_t ratio compared to subjects with normal hepatic function. Although the difference was not statistically significantly different, the mean 5-hydroxy dexlansoprazole AUC_t value for subjects with moderate hepatic impairment was approximately 50% lower than for subjects with normal hepatic function. Differences in dexlansoprazole sulfone t_{max} , C_{max} , AUC_t , and AUC_t ratios for subjects with impaired hepatic function were statistically significantly different and greater than those for subjects with normal hepatic function. This suggests that the increased dexlansoprazole sulfone plasma levels in the moderately hepatically impaired subjects were likely due to extrahepatic metabolism of higher levels of dexlansoprazole and/or a decrease in systemic elimination of this metabolite.

Safety Results:

No deaths or other serious or significant adverse events were reported in this study, and no subject prematurely discontinued due to an adverse event. Among all 24 subjects, 5 (21%) subjects experienced at least 1 treatment-emergent adverse event in this study (1 of 12 subjects with normal hepatic function and 4 of 12 subjects with moderate hepatic impairment). Two of 24 (8%) subjects experienced treatment-related adverse events (1 of 12 subjects with normal hepatic function [MedDRA PT Flatulence] and 1 of 12 subjects with moderate hepatic impairment [MedDRA PT Headache]). Both treatment-related adverse events were of mild severity.

Except for the expected clinical laboratory values in subjects with moderately impaired hepatic function, no subject had clinical laboratory, vital signs, and electrocardiogram results that were considered by the investigator to be clinically significant or were reported as adverse events.

Conclusions:

Following oral administration of a single 60 mg dose of dexlansoprazole MR, mean plasma exposure (AUC) of total and unbound dexlansoprazole in the hepatically impaired group was approximately 2-times greater compared to subjects with normal hepatic function. Although differences in the metabolite-to-parent drug AUC_t ratios between the hepatic function groups were found, the concentration of these inactive dexlansoprazole plasma metabolites were considered minor ($\leq 5\%$) when compared to parent drug. No dosage adjustment for dexlansoprazole MR doses up to 60 mg is likely to be necessary for subjects with mild or moderate hepatic impairment.

This study did not suggest any safety concerns associated with dexlansoprazole MR 60 mg capsules administered as a single dose in subjects with normal hepatic function or in subjects with moderate hepatic impairment.

Study T-P105-119 Age and Gender

Name of Company: TAP Pharmaceutical Products Inc					
Name of Finished Product: Dexlansoprazole MR Capsules					
Name of Active Ingredient: R-(+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole					
Title of Study: A Phase 1, Open-Label, Parallel Study to Evaluate the Effect of Gender and Age on the Pharmacokinetics and Safety of a Single Oral Dose of Dexlansoprazole MR 60 mg					
Investigator: (b) (4)					
Study Center: (b) (4)					
Publication (Reference): None					
Study Period:			Phase of Development: 1		
Date of First Dose: 03 February 2006					
Date of Last Procedure: 07 February 2006					
Objectives:					
The objectives of this study were:					
<ul style="list-style-type: none"> To assess the effect of age on the pharmacokinetics of a single oral dose of dexlansoprazole MR 60 mg To assess the effect of gender on the pharmacokinetics of a single oral dose of dexlansoprazole MR 60 mg To evaluate the safety following a single oral dose of dexlansoprazole MR 60 mg in young and elderly healthy subjects 					
Methodology:					
This was a Phase 1, open-label, parallel-group study to evaluate the effect of gender and age on the pharmacokinetics (PK) and safety of dexlansoprazole following administration of a 60 mg single oral dose of dexlansoprazole MR capsule. Six male and 6 female subjects 18 through 40 years of age, inclusive, and 6 male and 6 female subjects 65 through 80 years of age, inclusive, were enrolled as 4 groups in the study.					
Subjects who continued to meet the selection criteria were confined to the clinic in the afternoon of Day -1 until all study procedures were completed on Day 2. At approximately 0800 hours on Day 1, following a minimum 10-hour fast, subjects were administered a single dexlansoprazole MR 60-mg capsule.					
Blood and urine samples were collected for the analysis of drug concentrations and routine laboratory testing throughout the study.					
Subject safety was evaluated based upon reported adverse events, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and laboratory evaluations.					
Number of Subjects (Planned and Analyzed): 24 subjects were planned and enrolled: All 24 subjects were included in the safety and the pharmacokinetic analyses.					
Diagnosis and Main Criteria for Inclusion: Adult male and female subjects in general good health and between 18 to 40 years of age, inclusive, or between 65 to 80 years of age.					
Duration of Treatment: Subjects received a single dose of dexlansoprazole MR 60 mg-capsule.					
Test Product, Dose and Mode of Administration, and Lot Numbers:					
Test Product	Formulation	Dosage	Mode of Administration	Manufacturer	Lot Number
Dexlansoprazole MR Capsules	60-mg capsule	60 mg (single dose)	Oral	Takeda Pharmaceutical Company Limited	Z540R011

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<p>Criteria for Evaluation:</p> <p>Pharmacokinetics:</p> <p>Plasma concentrations of dexlansoprazole, 5-hydroxy dexlansoprazole (AG-1908, Metabolite VI) and dexlansoprazole sulfone (AG-1813, Metabolite VII) were determined and pharmacokinetic parameters were estimated, including the maximum (peak) plasma drug concentration (C_{max}), the time to maximum concentration (t_{max}), the apparent terminal elimination rate constant (λ_z), the apparent terminal elimination-phase half-life ($t_{1/2z}$), the area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable concentration (AUC_t), and the AUC from time zero to infinity (AUC_∞). In addition, the C_{max} and AUC_∞ ratios of metabolites to dexlansoprazole were calculated. The oral clearance (CL/F) and the apparent volume of distribution based on the terminal phase (V_z/F) for dexlansoprazole were also determined.</p> <p>Safety:</p> <p>Subject safety was monitored based upon reported adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory evaluations.</p>
<p>Statistical Methods:</p> <p>Pharmacokinetics:</p> <p>For each analyte (dexlansoprazole, 5-hydroxy dexlansoprazole and dexlansoprazole sulfone), plasma concentration data and pharmacokinetic parameters were tabulated and descriptive statistics were computed according to gender and age groups, and overall.</p> <p>A two-way analysis of variance (ANOVA) model was used to investigate the effects of gender and age on the dexlansoprazole PK parameters. This ANOVA model included factors for gender and age categories, and the interaction of gender and age categories. Age was treated as a categorical variable, with subjects either in the young (18 through 40 years, inclusive) or the elderly (65 through 80 years, inclusive) age categories. The pharmacokinetic parameters analyzed included t_{max}, λ_z, and the natural logarithms of C_{max}, AUC_t, and AUC_∞.</p> <p>Safety:</p> <p>Adverse events that started after the Day 1 dosing or worsened in severity after the Day 1 dosing were summarized by subject groups. The AEs were also tabulated with a breakdown by subject group and by event severity. Similar AE tabulations were performed on treatment-related AEs.</p> <p>Baseline, postdose, and mean change from baseline to postdose were summarized by subject groups for clinical laboratory variables and for vital signs. Subjects with laboratory or vital sign results that met the predefined criteria for potentially concerning values were identified.</p>
<p>Summary and Conclusions:</p> <p>Pharmacokinetic Results:</p> <p>The results of this study demonstrated that neither gender nor age had a statistically significant effect on C_{max} and AUC_∞ of dexlansoprazole following administration of a single oral dose of dexlansoprazole MR 60-mg capsule in healthy subjects. Dexlansoprazole was highly bound to human plasma proteins (95.6% to 97.4%) and the fraction unbound (FU) of dexlansoprazole was similar in male and female subjects, as well as in young and elderly subjects. Therefore, systemic exposure to the free dexlansoprazole was also expected to be similar between different gender and age groups. Although the mean half-life ($t_{1/2}$) value of dexlansoprazole in the elderly subjects was statistically significantly longer than that in the young subjects, this difference is unlikely to be clinically important. As such, neither gender nor age had a clinically relevant effect on the pharmacokinetics of dexlansoprazole following administration of a 60 mg single oral dose of dexlansoprazole MR in healthy subjects.</p> <p>No homozygous poor metabolizer of cytochrome P-450 -2C19 isoform (CYP2C19) was enrolled in this study. All subjects in this study were genotyped as either homozygous (n = 17) or heterozygous (n = 7) extensive metabolizers</p>

Summary and Conclusions:

Pharmacokinetic Results (Cont):

of CYP2C19. Furthermore, the estimated CL/F of dexlansoprazole was similar between heterozygous and homozygous extensive metabolizers of CYP2C19.

Even though there were statistically significant differences in the systemic exposures of dexlansoprazole metabolites between gender and age groups, these differences were not considered clinically relevant because both 5-hydroxy dexlansoprazole and dexlansoprazole sulfone are inactive metabolites with low circulating concentrations (systemic exposure <5% of the parent drug).

Safety Results:

Two (8%) of the 24 subjects enrolled in the study reported at least one AE. Both the subjects were elderly female subjects and experienced a mild, possibly treatment-related AE of headache. There were no deaths, serious adverse events (SAEs), or other significant AEs, and no subject withdrew from the study due to an AE.

There were no clinically important changes in physical examination results, vital signs, 12-lead ECG, and clinical laboratory evaluations.

Conclusions:

Based on the results obtained in this study, no dose adjustment for dexlansoprazole MR is required in different gender and age groups.

In this study, no gender or age based safety concerns associated with a single oral dose of dexlansoprazole MR 60-mg capsule in healthy subjects were observed.

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Study T-P105-132 Effect on the pharmacokinetics and pharmacodynamics of warfarin

Name of Company: TAP Pharmaceutical Products Inc			
Name of Finished Product: Dexlansoprazole MR Capsules			
Name of Active Ingredient: (+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole			
Title of Study: A Phase 1 Two-Way Crossover Study to Assess the Effect of Multiple Oral Doses of Dexlansoprazole MR (TAK-390MR) on the Single Oral Dose Pharmacokinetics and Pharmacodynamics of Warfarin.			
Investigator: A single investigator.			
Study Center: A single site in the United States of America.			
Publication (Reference): None			
Study Period:		Phase of Development: Phase 1	
Date of First Dose: 15 August 2006			
Date of Last Procedure: 18 September 2006			
Objective: The objective of this study was to evaluate the effect of multiple once-daily doses of dexlansoprazole modified-release (MR) (TAK-390MR) 90 mg on the pharmacokinetics and pharmacodynamics of a single warfarin 25 mg dose.			
Methodology: This was a Phase 1, single-center, double-blind, placebo controlled, randomized, two-way crossover study of dexlansoprazole MR or placebo for dexlansoprazole MR (placebo) with open-label warfarin (Coumadin). It was planned that approximately 20 adult male and female subjects, aged between 18 to 55 years, inclusive, in good health, would participate in this study. Subjects received both regimens (dexlansoprazole MR with warfarin and placebo with warfarin) in a crossover fashion as outlined below:			
		Regimens	
Sequence	Number of Subjects	Period 1	Period 2
1	10	Regimen A	Regimen B
2	10	Regimen B	Regimen A
Regimen A: Dexlansoprazole MR 90 mg once-daily for 11 consecutive days plus a single 25 mg warfarin oral dose on Day 6.			
Regimen B: Placebo once-daily for 11 consecutive days plus a single 25 mg warfarin oral dose on Day 6.			
There was a minimum 10-day washout interval between the last dose of study drug in Period 1 and the first dose of study drug in Period 2. Dosing began at 0800 hours following a minimum 10-hour fast on Days 1 through 11 of each period. A standard breakfast, lunch, dinner, and snack were served 1, 4, 9, and 13 hours post dexlansoprazole dose on Days 1 through 11 of each period.			
Blood samples for laboratory safety analysis were drawn predose on Day -1 of Period 1 to ensure subjects still met eligibility requirements and for genotyping of subject's CYP2C19 and CYP2C9 genes. Blood samples for the quantitation of dexlansoprazole were collected on Day 6 at predose (0 hr) and at 4 and 24 hours following the administration of dexlansoprazole MR dose in each period. Blood samples for the quantitation of R- and S-warfarin were collected on Day 6 at predose (0 hr) and up to 144 hours following administration of warfarin in each period.			
Blood samples were also obtained following administration of warfarin 25 mg on Day 6 of each study period and the pharmacodynamics (PD) of warfarin were evaluated for 144 hours postdose. Anticoagulant activity was monitored using the international normalized ratio (INR).			
Number of Subjects (Planned and Analyzed): Twenty (20) healthy subjects were planned, 19 subjects were enrolled at one study site in the United States. Nineteen subjects were included in the safety analysis and 18 subjects were included in the pharmacokinetic (PK)/PD analysis.			

Diagnosis and Main Criteria for Inclusion: Healthy male or female subjects aged between 18 and 55 years, inclusive, on Day 1 of Period 1.					
Duration of Treatment: During the 2 crossover periods, each subject received either 90 mg dexlansoprazole MR or placebo daily for 11 consecutive days. On Day 6 of each period, subjects were coadministered a single dose of 25 mg warfarin immediately following the dose of placebo or 90 mg dexlansoprazole MR. There was a washout interval of at least 10 days between the last dose of study drug in Period 1 and the first dose of study drug in Period 2.					
Test Product, Dose, Mode of Administration, and Lot Number:					
Study Drug	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Drug Product Lot Number
Dexlansoprazole MR	90 mg Capsule	90 mg	Oral	Takeda Pharmaceutical Company	Z540S042
Reference Therapies, Doses, Modes of Administration, and Lot Numbers:					
Study Drug	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Drug Product Lot Number
Warfarin (Coumadin)	10 mg Tablet 5 mg Tablet	25 mg	Oral	Bristol-Myers Squibb Company	ETL551A EUA064A
Placebo for Dexlansoprazole MR	Capsule	NA	Oral	Takeda Pharmaceutical Company	Z540T041
Criteria for Evaluation:					
<p>Pharmacokinetics: Pharmacokinetic parameters for R- and S-warfarin in plasma were estimated using standard noncompartmental methods. The PK parameters included: the observed maximum (peak) plasma drug concentration (C_{max}), the time to reach the observed maximum (peak) plasma drug concentration (t_{max}), the apparent terminal elimination-rate constant (λ_z), the apparent terminal elimination-phase half-life ($t_{1/2}$), and area under the plasma concentration-time curve (AUC) from time zero to the last measurable concentration (AUC_t) and to infinity (AUC_{∞}). In addition, the oral clearance (CL/F) and apparent volume of distribution during the terminal phase (V_z/F) for R- and S-warfarin were estimated. A limited number of plasma samples for the quantification of dexlansoprazole were also obtained in this study in order to confirm that all subjects received the correct oral doses of dexlansoprazole MR or placebo according to the sequence specified in the randomization schedule.</p>					
<p>Pharmacodynamics: Prothrombin time (PT) was measured and reported as the INR and was considered the primary PD variable. The PD parameters that were analyzed were the area under the INR-time curve from time 0 to 144 hours postdose (INR_{144}) and the maximum INR value observed from time 0 to 144 hours postdose (INR_{max}) following the Day 6 warfarin administration.</p>					
<p>Safety: Subject safety was evaluated based upon reported adverse events (AEs), physical examinations, daily vital signs, electrocardiograms (ECGs), and safety laboratory tests. Safety lab assessments (including chemistry, hematology and urinalysis) were drawn at screening and Days -1, 7, and 12 of each period.</p>					

Statistical Methods:**Pharmacokinetics:**

For each regimen, dexlansoprazole and R- and S-warfarin plasma concentration data, and R- and S-warfarin PK parameter estimates were tabulated and descriptive statistics computed. Analyses of variance (ANOVAs) were performed on t_{max} , and the natural logarithms of C_{max} , AUC_0-1 , and $AUC_{0-\infty}$. The effect of dexlansoprazole MR was assessed via 90% confidence intervals for the ratio of dexlansoprazole plus warfarin to placebo plus warfarin central values for warfarin C_{max} and AUCs. A conclusion of no effect of dexlansoprazole on the pharmacokinetics of warfarin was to be made if the 90% confidence intervals were within (0.80, 1.25) for R- and S-warfarin C_{max} and AUCs.

Pharmacodynamics:

Descriptive statistics on the INR measured at each blood sample collection timepoint are presented for each regimen. The statistical model for testing the effect of dexlansoprazole MR on the warfarin PD was an analysis of variance on INR_{144} and INR_{max} .

Safety:

Adverse events that started after the first dose, or worsened in severity, were summarized for each regimen. Similar AE tabulations were performed on those events assessed by the investigator as related (possibly or definitely) to study drug. Baseline, postdose, and change from baseline to postdose laboratory values were summarized utilizing descriptive statistics for each regimen.

Vital signs (systolic/diastolic blood pressure and pulse rate) were summarized for each regimen utilizing descriptive statistics for baseline and postdose, and change from baseline to postdose values.

Electrocardiogram (ECG) comments were coded by the sponsor using the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary. Findings present at both baseline and postdose were not included in the analysis. The clinical significance of ECG changes from baseline were assessed by the investigator and listed by subject.

Summary and Conclusions:**Baseline Demographics:**

Baseline demographic characteristics for all subjects are summarized in the table below.

Variable	All Subjects N=19
Gender n (%)	
Male	19 (100)
Female	0
Ethnicity n (%)	
Hispanic or Latino	1 (5.3)
Not Hispanic or Latino	18 (94.7)
Race n (%)	
American Indian/Alaska Native	1 (5.3)
Black	5 (26.3)
White	9 (47.4)
Multiracial	4 (21.1)
Age (yr)	
Mean (Standard Deviation)	33.7 (9.31)

Summary and Conclusions (Cont):
Pharmacokinetic Results:
 Noncompartmental PK parameter estimates for R-warfarin and S-warfarin following administration of a single 25 mg oral dose of warfarin with either dexlansoprazole MR 90 mg or placebo are summarized in the table below.

Regimen		t_{max} (h)	C_{max} ($\mu\text{g/mL}$)	AUC_t ($\mu\text{g}\cdot\text{h/mL}$)	AUC_{∞} ($\mu\text{g}\cdot\text{h/mL}$)	$t_{1/2}^a$ (h)	CL/F (mL/h)	V_z/F (L)
R-Warfarin								
Regimen A	N	18	18	18	18	18	18	18
	Mean	1.03	1.65	73.03	85.07	49.04 (46.75)	304.69	20.96
	CV (%)	170	15	14	19	22	21	17
Regimen B	N	18	18	18	18	18	18	18
	Mean	1.76	1.52	71.05	82.15	48.81 (46.29)	314.29	21.63
	CV (%)	203	13	14	18	22	19	20
S-Warfarin								
Regimen A	N	18	18	18	18	18	18	18
	Mean	0.67	1.72	50.11	54.54	42.06 (40.48)	488.49	29.02
	CV (%)	37	17	23	26	21	26	25
Regimen B	N	18	18	18	18	18	18	18
	Mean	0.95	1.58	47.92	51.76	40.12 (38.90)	510.37	29.12
	CV (%)	47	16	21	24	18	25	26

CV (%) = percent coefficient of variation.

a Arithmetic mean (harmonic mean).

The mean plasma warfarin concentration-time profiles following administration of a single 25 mg oral dose of warfarin with dexlansoprazole MR 90 mg (Regimen A) or placebo (Regimen B) were nearly superimposable. Mean t_{max} , C_{max} , AUC_t , AUC_{∞} , and $t_{1/2}$ values estimated for S-warfarin were similar between Regimens A and B. In addition, the estimated CL/F and V_z/F values for S-warfarin did not appear to be different after the administration of warfarin 25 mg with either dexlansoprazole MR 90 mg or placebo. Furthermore, no apparent differences were observed in the pharmacokinetic parameter estimates for R-warfarin after administration of warfarin with either 90 mg dexlansoprazole MR or placebo.

The statistical assessment of effect of dexlansoprazole MR on the PK of warfarin was performed via 90% confidence intervals for the ratio of central values of R- and S-warfarin C_{max} and AUCs. The estimated ratios of central values and 90% confidence intervals for the ratios are summarized in the table below.

Parameter	Point Estimate	90% Confidence Interval
R-Warfarin		
C_{max}	0.93	(0.8601 – 1.0027)
AUC_t	0.97	(0.9544 – 0.9936)
AUC_{∞}	0.97	(0.9433 – 0.9923)
S-Warfarin		
C_{max}	0.93	(0.8397 – 1.0199)
AUC_t	0.96	(0.9325 – 0.9917)
AUC_{∞}	0.95	(0.9232 – 0.9860)

Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm transformed data.

Summary and Conclusions (Cont):**Pharmacokinetic Results (Cont):**

The 90% confidence intervals for the ratio of the central values between Regimens A and B were within the bioequivalence range of 0.80 to 1.25 for the C_{max} , AUC_{0-6} , and AUC_{0-24} for both R- and S-warfarin.

A limited number of plasma samples for the quantification of dexlansoprazole were also obtained in this study.

Based on this data, it appears that all subjects received the oral doses of dexlansoprazole MR or placebo according to the sequence specified in the randomization schedule.

Pharmacodynamic Results:

A summary of warfarin PD parameters are presented in the table below. The small differences between Regimens A and B for INR_{144} and INR_{max} PD parameters were not statistically or clinically significant, indicating that 90 mg dexlansoprazole MR administration does not interfere with the anticoagulant effects of warfarin.

Regimen		INR_{144} (N=18)	INR_{max} (N=18)
Regimen A	Mean	184.404	1.622
	SD	23.949	0.284
Regimen B	Mean	184.798	1.656
	SD	23.927	0.311
Difference in Least Square Means (Regimen A - Regimen B)		0.184	-0.019
p-value		0.910	0.362

Regimen A: 90 mg dexlansoprazole MR once-daily for 11 consecutive days plus a single 25 mg warfarin oral dose on Day 6.

Regimen B: Placebo once-daily for 11 consecutive days plus a single 25 mg warfarin oral dose on Day 6.

Safety Results:

Five of the 19 enrolled subjects (26%) reported at least one AE during the study. The percentage and number of subjects who experienced at least one AE by dosing regimen were: 11% (2/19) for Regimen A and 17% (3/18) for Regimen B. No AE was reported by >1 subject in either of the 2 regimens. There were no trends observed in AEs associated with the administration of either 90 mg dexlansoprazole MR alone, or with 25 mg warfarin, in this study. No deaths or other serious AEs occurred, and no subject prematurely discontinued the study due to an AE. No consistent, unexpected, clinically important changes in laboratory test results, vital signs, physical examinations, or ECG changes were observed. In this study of healthy subjects, no safety concerns were associated with administration of 90 mg dexlansoprazole MR, either alone, or with a single dose of 25 mg warfarin.

Conclusions:

Multiple once-daily oral doses of 90 mg dexlansoprazole MR in healthy subjects had no effect on the pharmacokinetics or pharmacodynamics of warfarin. Therefore, no dosage adjustment of warfarin is required when given concomitantly with dexlansoprazole MR. The results also indicate that dexlansoprazole does not affect hepatic CYP2C9 activities in humans and, therefore, will not alter the metabolism of drugs metabolized by this enzyme.

In this study of healthy subjects, no safety concerns were associated with administration of multiple once-daily doses of dexlansoprazole MR, either alone, or with a single dose of 25 mg warfarin.

Study T-P105-133 Effect on the pharmacokinetics of phenytoin

Name of Company: TAP Pharmaceutical Products Inc			
Name of Finished Product: Dexlansoprazole MR Capsules			
Name of Active Ingredient: (+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl} sulfinyl]-1H-benzimidazole			
Title of Study: A Phase 1, Double-Blind, Placebo-Controlled, Two-way Crossover Study to Assess the Effect of Multiple Oral Doses of 90 mg Dexlansoprazole MR on the Pharmacokinetics of Phenytoin Following a Single Oral Dose of 250 mg Phenytoin.			
Investigator: Single Investigator			
Study Center: A single site in the United States of America.			
Publication (Reference): None			
Study Period:		Phase of Development: Phase 1	
Date of First Dose: 19 July 2006			
Date of Last Procedure: 07 September 2006			
Objective: To evaluate the effect of multiple once-daily oral doses of 90 mg dexlansoprazole modified release (MR) (TAK-390MR) on the pharmacokinetics of a single oral dose of 250 mg phenytoin.			
Methodology: This was a Phase 1, single-center, double-blind, placebo-controlled, randomized, two-way crossover study of dexlansoprazole MR, or placebo for dexlansoprazole MR (placebo), with open-label phenytoin. Healthy subjects who met the study eligibility criteria were selected to participate in this study. Subjects received both regimens (dexlansoprazole MR with phenytoin and placebo with phenytoin) in a crossover fashion as outlined below:			
Sequence	Number of Subjects	Regimens	
		Period 1	Period 2
1	8	Regimen A	Regimen B
2	8	Regimen B	Regimen A
Regimen A: 90 mg dexlansoprazole MR once-daily for 9 consecutive days plus a single oral dose of 250 mg phenytoin (10 mL of 125 mg/5 mL Dilantin-125 oral suspension administered via oral syringe) on Day 6			
Regimen B: Placebo once-daily for 9 consecutive days plus a single oral dose of 250 mg phenytoin (10 mL of 125 mg/5 mL Dilantin-125 oral suspension administered via oral syringe) on Day 6			
There was a washout interval of at least 7 days between the last dose of study drug in Period 1 and the first dose of study drug in Period 2. One hour after study drug dosing on Days 1 through 9, subjects received a standardized breakfast. Standardized lunch, dinner, and a snack were served at scheduled times. The meals provided were identical in each period. Upon completion of the study, each subject had received 9 doses of 90 mg dexlansoprazole MR, 9 doses of placebo, and 2 doses of 250 mg phenytoin.			
Blood samples were collected beginning predose on Day 6 of each period until 96 hours postdose, to determine plasma concentration of phenytoin. A limited number of blood samples for the determination of plasma concentrations of dexlansoprazole were also collected on Day 6 of each period. In addition, a single blood sample (6 mL) was drawn on Day -1 for genotyping of the CYP2C19 and CYP2C9 genes.			
Number of Subjects (Planned and Analyzed): Sixteen (16) subjects were planned, enrolled, and analyzed at one study site in the United States.			
Diagnosis and Main Criteria for Inclusion: Healthy male or female subjects aged between 18 and 55 years, inclusive.			
Duration of Treatment: During the 2 crossover periods, each subject received either 90 mg dexlansoprazole MR or placebo daily for 9 consecutive days. On Day 6 of each period, subjects were coadministered a single dose of 250 mg phenytoin immediately following the dose of placebo or 90 mg dexlansoprazole MR. There was a washout interval of at least 7 days between the last dose of study drug in Period 1 and the first dose of study in Period 2.			

Study Drug	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Drug Product Lot Number
Dexlansoprazole MR	90 mg Capsule	90 mg	Oral	Takeda Pharmaceutical Company	Z540S042
Reference Therapy, Dose, Mode of Administration, and Lot Number:					
Study Drug	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Drug Product Lot Number
Phenytoin (Dilantin-125)	125 mg/5 mL Oral Suspension	250 mg	Oral	Pfizer US Pharmaceuticals	48025L
Placebo for Dexlansoprazole MR	Capsule	Not applicable	Oral	Takeda Pharmaceutical Company	Z540T022
Criteria for Evaluation:					
<p>Pharmacokinetics: The following pharmacokinetic parameters for phenytoin in plasma were estimated using standard noncompartmental methods: the observed peak plasma concentration (C_{max}), the time to reach the observed peak plasma concentration (t_{max}), the apparent terminal elimination-rate constant (λ_z), the apparent terminal elimination-phase half-life ($t_{1/2z}$), and area under the plasma concentration-time curve (AUC) from time zero to the last measurable concentration (AUC_t), and to infinity (AUC_{∞}), the oral clearance (CL/F), and apparent volume of distribution (V_z/F).</p> <p>Safety: Subject safety was evaluated based upon reported adverse events (AEs), physical examinations, vital signs, electrocardiograms (ECGs), and safety laboratory tests. Standard safety laboratory assessments (including chemistry, hematology, and urinalysis) were followed for this study. Samples were drawn at the Screening Visit, and on Days -1 and 10 of each period.</p>					
Statistical Methods:					
<p>Pharmacokinetics: For each regimen, phenytoin plasma concentration data, and phenytoin PK parameter estimates were tabulated and descriptive statistics computed. For Regimen A, dexlansoprazole plasma concentration data was tabulated and descriptive statistics computed.</p> <p>Analyses of variance (ANOVA) were performed on phenytoin t_{max}, and the natural logarithms of C_{max}, AUC_t, and AUC_{∞}, with factors for sequence, subjects nested within sequence, period, and regimen. The factor of subjects nested within sequence was considered random, and all other factors were fixed. The effect of dexlansoprazole MR on phenytoin PK was assessed via 90% confidence intervals for the ratio of dexlansoprazole plus phenytoin to placebo plus phenytoin central values for phenytoin C_{max} and AUCs. These confidence intervals were determined by exponentiating the endpoints of 90% confidence intervals for the difference of natural logarithm regimen means obtained within the framework of the ANOVA model. A conclusion of no effect of dexlansoprazole MR on the pharmacokinetics of phenytoin was to be made if the 90% confidence intervals were within (0.80, 1.25) for phenytoin C_{max} and AUCs.</p> <p>Safety: All subjects who were enrolled in the study and took at least one dose of study drug were included in the safety analyses. Adverse events that started after the first dose, or worsened in severity, were summarized for each regimen. Baseline, postdose, and change from baseline to postdose laboratory values were summarized utilizing descriptive statistics for each regimen.</p>					

Statistical Methods (Cont):							
Safety (Cont)							
Vital signs (systolic/diastolic blood pressure and pulse rate) were summarized for each regimen utilizing descriptive statistics for baseline and postdose, and change from baseline to postdose values.							
Electrocardiogram comments were coded by the sponsor using the Medical Dictionary of Regulatory Activities (MedDRA) coding dictionary. The number and percentage of subjects with treatment-emergent findings were summarized by regimen. The clinical significance of ECG changes from baseline were assessed by the investigator and listed by subject.							
Summary and Conclusions:							
Baseline Demographics:							
Baseline demographic characteristics for all subjects are summarized in the table below:							
Variable	All Subjects N=16						
Gender n (%)							
Male	14 (87.5)						
Female	2 (12.5)						
Ethnicity n (%)							
Hispanic or Latino	2 (12.5)						
Not Hispanic or Latino	14 (87.5)						
Race n (%)							
Black	6 (37.5)						
White	10 (62.5)						
Age (yr)							
Mean (SD)	25.8 (4.61)						
Pharmacokinetics Results:							
Noncompartmental pharmacokinetic parameter estimates for phenytoin following a single 250 mg oral dose of phenytoin are summarized below:							
	t_{max} (h)	C_{max} ($\mu\text{g/mL}$)	AUC_t ($\mu\text{g}\cdot\text{h/mL}$)	AUC_{∞} ($\mu\text{g}\cdot\text{h/mL}$)	V_z/F (L)	CL/F (L/h)	$t_{1/2}^a$ (h)
90 mg Dexlansoprazole MR & 250 mg Phenytoin (Regimen A)							
N	16	16	16	16	16	16	16
Mean	7.56	2.85	111.90	113.99	44.60	2.35	13.55 (13.14)
SD	5.33	0.61	27.04	28.53	10.51	0.73	2.46
CV (%)	70	21	24	25	24	31	18
Placebo & 250 mg Phenytoin (Regimen B)							
N	16	16	16	16	16	16	16
Mean	9.16	2.92	113.41	115.62	43.75	2.29	13.65 (13.12)
SD	5.42	0.60	26.18	27.71	9.25	0.58	2.92
CV (%)	59	20	23	24	21	25	21
CV (%) = percent coefficient of variation.							
a Arithmetic mean (harmonic mean).							

Summary and Conclusions (Cont):**Pharmacokinetics Results (Cont):**

Following oral administration of a single 250 mg dose of phenytoin to subjects who received placebo or dexlansoprazole MR, the average time to achieve maximum phenytoin plasma concentrations, and the mean phenytoin C_{max} and AUC values were similar between the 2 regimens. The mean plasma concentration-time profiles of phenytoin were nearly superimposable in the placebo and dexlansoprazole MR regimens. In addition, the estimated CL/F , V_z/F , and $t_{1/2}$ values for phenytoin did not appear to be different when administered with dexlansoprazole or placebo.

The statistical assessment of differences in the pharmacokinetic parameter estimates of phenytoin obtained after dosing with either dexlansoprazole MR 90 mg or placebo was performed via 90% confidence intervals for the ratios of the central values for C_{max} , AUC_0-t , and $AUC_{0-\infty}$. These data are presented in the table below:

Bioavailability of Phenytoin with Dexlansoprazole MR Relative to that of Phenytoin with Placebo		
Parameter	Point Estimate	90% Confidence Interval
C_{max}	0.9726	(0.8937 - 1.0584)
AUC_0-t	0.9820	(0.9380 - 1.0282)
$AUC_{0-\infty}$	0.9811	(0.9363 - 1.0281)

Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm transformed data.

The 90% confidence intervals for the ratio of the central values of phenytoin C_{max} and AUCs were within the 0.80 to 1.25 bioequivalency range indicating an absence of an effect of 90 mg dexlansoprazole MR on phenytoin pharmacokinetics.

Safety Results:

Eight (50%) of the 16 subjects enrolled reported at least one AE during the study, including one subject (6%) who experienced a treatment-related AE (flatulence on Day 2 of Regimen A). The percentage and number of subjects who experienced at least one AE by dosing regimen were 31% (5/16) for Regimen A and 25% (4/16) for Regimen B. All AEs were mild in severity and there were no deaths, serious adverse events, or other significant AEs, and no subject prematurely discontinued the study due to an AE. There were no trends observed in AEs associated with the administration of either 90 mg dexlansoprazole MR alone, or with 250 mg phenytoin, in this study. No consistent, clinically important changes in laboratory test results, vital signs, physical examinations, or ECG changes were observed. In this study of healthy subjects, no safety concerns were associated with administration of dexlansoprazole MR, either alone, or with a single dose of 250 mg phenytoin.

Conclusions:

Multiple daily 90 mg oral doses of dexlansoprazole MR in healthy subjects had no effect on the pharmacokinetics of phenytoin. Therefore, no dosage adjustment of phenytoin is required when given concomitantly with dexlansoprazole MR. The results also indicate that dexlansoprazole does not appear to affect hepatic CYP2C19 or CYP2C9 activities in humans and therefore will not alter the metabolism of drugs that are metabolized by these enzymes.

In this study of healthy subjects, no safety concerns were associated with administration of multiple once-daily doses of dexlansoprazole MR either alone, or with a single 250 mg phenytoin dose.

Study T-P105-134 Effect on the pharmacokinetics of diazepam

Name of Company: TAP Pharmaceutical Products Inc			
Name of Finished Product: Dexlansoprazole MR Capsules			
Name of Active Ingredient: (+)-2-[(R)-{[3-Methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole			
Title of Study: A Phase 1, Double-Blind, Placebo-Controlled, Two-Way Crossover Study to Assess the Effect of Multiple Oral Doses of Dexlansoprazole MR on Diazepam Pharmacokinetics Following a Single Oral Dose of Diazepam			
Investigator: 1 investigator			
Study Center: Single investigative site in the United States of America			
Publication (Reference): None			
Study Period:		Phase of Development: 1	
Date of First Dose: 12 May 2006			
Date of Last Procedure: 22 June 2006			
Objective: The objective of this study was to evaluate the effect of multiple, once-daily (QD) doses of 90 mg of dexlansoprazole modified release (MR [TAK-390MR]) on the pharmacokinetics of a single, oral dose of 5 mg of diazepam.			
Methodology: This was a Phase 1, single-center, double-blind, placebo-controlled, randomized, two-period crossover study with open-label administration of diazepam. Healthy subjects received a different dosing regimen during each period of the study, in addition to the open-label diazepam. Twenty subjects were randomly assigned to the sequence in which they received each of the 2 different regimens, as summarized in the following table.			
Regimen Sequences			
Sequence	Number of Subjects	Period 1	Period 2
1	10	Regimen A Dexlansoprazole MR 90 mg QD (Days 1 to 11) plus 5 mg of diazepam (Day 6)	Regimen B Placebo for dexlansoprazole MR QD (Days 1 to 11) plus 5 mg of diazepam (Day 6)
2	10	Regimen B Placebo for dexlansoprazole MR QD (Days 1 to 11) plus 5 mg of diazepam (Day 6)	Regimen A Dexlansoprazole MR 90 mg QD (Days 1 to 11) plus 5 mg of diazepam (Day 6)
On Day -1 of each period, subjects were confined to the clinical testing facility, and they remained confined until all study procedures were completed on Day 12 of each period. During each period, dosing began at approximately 0800 hours on Days 1 through 11. On Day 6 of each period, 5 mg of diazepam was co-administered with either 90 mg of dexlansoprazole MR or placebo. A washout interval of at least 7 days separated the last dose of Period 1 from the first dose of Period 2. Safety was monitored through adverse event (AE) reports, concomitant medication usage, physical examinations, vital sign assessments, and laboratory evaluations. The pharmacokinetic profiles of diazepam and its major circulating metabolite, nordiazepam, were assessed through blood sampling on Days 6 through 12 of each period. The plasma concentrations of diazepam and nordiazepam were determined using a validated assay of liquid chromatography tandem mass spectrometry (LC-MS/MS). Plasma concentrations of dexlansoprazole were assessed through blood sampling on Days 6 and 7 of each period, and concentrations were determined using a validated LC-MS/MS assay for lansoprazole.			
Number of Subjects (Planned and Analyzed): Twenty subjects were planned and enrolled. Thirteen (65%) subjects were male, and 7 (35%) were female. Seventeen (85%) subjects were white, and 3 (15%) were black. One (5%) subject was Hispanic or Latino. The mean age of the subjects was 29.6 years (standard deviation: \pm 8.25 years). Nineteen subjects were included in the pharmacokinetic analyses of diazepam and nordiazepam, and 20 subjects were included in the safety analyses.			

Diagnosis and Main Criteria for Inclusion: Male and female subjects between 18 and 55 years of age, inclusive, and in general good health.					
Duration of Treatment: Over the 2 crossover periods, each subject was to receive 90 mg of dexlansoprazole MR for 11 consecutive days and placebo for dexlansoprazole MR (placebo) QD for 11 consecutive days. A single dose of 5 mg of diazepam was administered on Day 6 of each period. A washout interval of at least 7 days was to separate the last dose in Period 1 and the first dose in Period 2.					
Test Product, Dose and Mode of Administration, and Lot Number:					
	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Drug Product Lot Number
Dexlansoprazole MR	One 90-mg Capsule	90 mg QD for 11 days	Oral	Takeda Pharmaceutical Company Limited	Z540S042
Reference Therapy, Dose and Mode of Administration, and Lot Number:					
	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Drug Product Lot Number
Placebo	One 0-mg Capsule	Not Applicable	Oral	Takeda Pharmaceutical Company Limited	Z540T041
Diazepam	One 5-mg Tablet	5 mg once each period	Oral	Roche Laboratories Inc	U2051
Criteria for Evaluation:					
Pharmacokinetics:					
Pharmacokinetic parameters for diazepam in plasma were estimated using standard noncompartmental methods. The pharmacokinetic parameters estimated for diazepam included: the maximum (peak) plasma drug concentration (C_{max}), the time to maximum (peak) drug concentration (t_{max}), the apparent terminal elimination rate constant (λ_2), the apparent terminal elimination-phase half-life ($t_{1/2\lambda}$), area under the plasma concentration-time curve (AUC) from time zero to the time of the last measurable concentration (AUC_t) and to infinity (AUC_∞), the oral clearance (CL/F), and the apparent volume of distribution during the terminal phase (V_z/F). Pharmacokinetic parameters estimated for nordiazepam included: t_{max} , C_{max} , AUC_t , and the ratio of nordiazepam-to-diazepam AUC_t .					
Safety:					
Safety was monitored by assessing AEs, concomitant medication usage, clinical laboratory variables, and vital signs.					
Statistical Methods:					
Pharmacokinetics:					
Descriptive statistics for the plasma concentrations and for each of the pharmacokinetic parameters for diazepam and nordiazepam were computed for each regimen. Descriptive statistics were also computed for dexlansoprazole plasma concentrations on Day 6 of each period. To assess the effect of multiple QD doses of 90 mg of dexlansoprazole on the pharmacokinetics of diazepam, analyses of variance were performed on diazepam and nordiazepam t_{max} and the natural logarithms of C_{max} , AUC_t , and AUC_∞ (diazepam only), using a model with factors of sequence, subjects nested within sequence, period, and regimen. The factor of subjects within sequence was treated as random, and all other factors were fixed. The effect of dexlansoprazole on diazepam and nordiazepam pharmacokinetics was assessed by point estimates and 90% confidence intervals for the ratios of dexlansoprazole plus diazepam to placebo plus diazepam central values for diazepam or nordiazepam C_{max} , AUC_t , and AUC_∞ (diazepam only). If the 90% confidence intervals for C_{max} , AUC_t , and AUC_∞ (diazepam only) were completely contained within the "no effect" range of 0.80 and 1.25 for diazepam and nordiazepam, a conclusion of "no effect" was to be made.					

Safety:
All subjects who received at least 1 dose of study drug were included in the analyses of safety. Treatment-emergent AEs were summarized for each regimen and overall. Baseline and postdose values and mean change from baseline to postdose were summarized by regimen for clinical laboratory variables and for vital signs. Subjects with a laboratory or vital sign result that met predefined criteria for potentially clinically important values were identified.

Summary and Conclusions:

Pharmacokinetic Results:

Noncompartmental pharmacokinetic parameter estimates for diazepam and nordiazepam following a single oral dose of 5 mg diazepam are summarized below:

Summary of Pharmacokinetic Parameter Estimates for Diazepam and Nordiazepam Following a Single Oral Dose of 5 mg of Diazepam during Each Regimen

Regimen	Measure	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_{∞} (ng·h/mL)	V_z/F (L)	CL/F (L/h)	$t_{1/2z}$ ^a (h)	AUC_t Ratio ^b
Diazepam									
A	N	19	19	19	19	19	19	19	NA
	Mean	0.91	165.82	3473.56	4395.43	100.46	1.31	61.18 (48.37)	NA
	SD	0.41	38.86	936.74	1705.51	32.40	0.51	33.41	NA
	%CV	45	23	27	39	32	39	55	NA
B	N	19	19	19	19	19	19	19	NA
	Mean	0.75	186.05	3388.61	4047.62	93.03	1.37	51.49 (42.69)	NA
	SD	0.37	53.61	863.54	1262.22	29.61	0.47	19.67	NA
	%CV	50	29	25	31	32	34	38	NA
Nordiazepam									
A	N	19	19	19	ND	ND	ND	ND	19
	Mean	83.36	20.64	2217.24	ND	ND	ND	ND	0.69
	SD	36.31	6.62	551.21	ND	ND	ND	ND	0.28
	%CV	44	32	25	ND	ND	ND	ND	40
B	N	19	19	19	ND	ND	ND	ND	19
	Mean	74.54	21.48	2350.33	ND	ND	ND	ND	0.74
	SD	28.98	6.68	544.17	ND	ND	ND	ND	0.26
	%CV	39	31	23	ND	ND	ND	ND	35

Note: Regimen A = 90 mg of dexlansoprazole MR QD for 11 days plus a single dose of 5 mg of diazepam, and Regimen B = placebo QD for 11 days plus a single dose of 5 mg of diazepam.

NA = not applicable; ND = not determinable.

a Arithmetic mean (harmonic mean); b ratio of nordiazepam AUC_t /diazepam AUC_t .

Following administration of a single 5 mg dose of diazepam to subjects that received placebo or 90 mg of dexlansoprazole MR, the average time to achieve maximum diazepam or nordiazepam plasma concentrations and the mean diazepam or nordiazepam C_{max} and AUC values were generally similar between the 2 regimens. The mean plasma concentration-time profiles of diazepam or nordiazepam from the placebo and dexlansoprazole regimens were nearly superimposable. In addition, the estimated values for CL/F and V_z/F and the harmonic means of $t_{1/2z}$ for diazepam were similar when diazepam was administered with either dexlansoprazole MR or placebo.

A limited number plasma samples for the quantitation of dexlansoprazole were obtained in this study. Based on the assay results, all subjects received the regimens in the proper sequence, according to the randomization schedule.

The statistical assessment of the effect of 90 mg of dexlansoprazole MR on the pharmacokinetics of diazepam and nordiazepam was performed via 90% confidence intervals for the central value ratios for C_{max} , AUC_t , and AUC_{∞} (diazepam only). The results of this assessment are presented in the following table.

Bioavailability of Diazepam and Nordiazepam with Concomitant Administration of Dexlansoprazole MR, Relative to Concomitant Administration of Placebo

Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
Diazepam		
C_{max}	0.8881	(0.8255 – 0.9555)
AUC_t	1.0206	(0.9860 – 1.0564)
AUC_{∞}	1.0646	(1.0126 – 1.1193)
Nordiazepam		
C_{max}	0.9524	(0.9140 – 0.9923)
AUC_t	0.9284	(0.8804 – 0.9789)

Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm-transformed data.

The 90% confidence intervals for the ratio of the central values of diazepam and nordiazepam C_{max} and AUCs were within the 0.80 to 1.25 range, indicating an absence of an effect of dexlansoprazole MR on diazepam and nordiazepam pharmacokinetics.

Safety Results:

No clinically important difference in safety results was observed between the dexlansoprazole MR plus diazepam and the placebo plus diazepam dosing regimens. Fourteen subjects (70%) experienced at least 1 treatment-emergent AE during their participation in the study. The number (%) of subjects experiencing an AE during a given dosing regimen was 10 (50%) during Regimen A (90 mg of dexlansoprazole MR plus diazepam) and 9 (47%) during Regimen B (placebo plus diazepam). The AEs experienced by ≥ 2 subjects during either regimen, based on the Medical Dictionary for Regulatory Activities (MedDRA) High Level Term, were Disturbances in Consciousness Not Elsewhere Classified (NEC, MedDRA Preferred Term [PT] of Somnolence, 3 subjects Regimen A and 5 subjects Regimen B), Headaches NEC (4 subjects Regimen A and 1 subject Regimen B), Neurological Signs and Symptoms NEC (MedDRA PT of Dizziness, 1 subject Regimen A and 2 subjects Regimen B), and Asthenic Conditions (MedDRA PTs of asthenia and fatigue, 1 subject Regimen A and 2 subjects Regimen B). No deaths occurred, but 1 subject had a serious adverse event (hospitalization for surgery due to a perforated appendix) that resulted in the subject's premature discontinuation from the study. The perforated appendix, which was considered not related to administration of study drug, occurred during the washout interval following Period 1; the subject had received Regimen A during Period 1. No consistent, clinically important changes in laboratory test results, vital signs, or physical examinations were observed.

In this study, no safety concerns were associated with the administration of dexlansoprazole MR alone or with 5 mg of diazepam to healthy subjects.

Conclusions:

Multiple, once-daily oral doses of 90 mg of dexlansoprazole MR administered for 11 consecutive days to healthy subjects had no effect on the pharmacokinetics of diazepam or nordiazepam. These results indicate that dexlansoprazole does not affect hepatic cytochrome P450 isozyme 2C19 activity in humans and, therefore, will not alter the metabolism of other drugs that are metabolized by this enzyme.

In this study, no safety concerns were associated with the administration of dexlansoprazole MR alone or with 5 mg of diazepam to healthy subjects.

Study T-P105-139 Effect on the pharmacokinetics of theophylline

Name of Company: TAP Pharmaceutical Products Inc			
Name of Finished Product: Dexlansoprazole MR Capsules			
Name of Active Ingredient: R-(+)-2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole			
Title of Study: A Phase 1, Double-Blind, Placebo-Controlled, Two-way Crossover Study to Assess the Effect of Multiple Oral Doses of Dexlansoprazole MR on the Pharmacokinetics of Theophylline Following a Single Intravenous Dose of Aminophylline			
Investigator: 1 investigator			
Study Center: single site in the United States			
Publication (Reference): none			
Study Period:		Phase of Development: 1	
Date of First Dose: 15 June 2006			
Date of Last Procedure: 16 July 2006			
Objective: To evaluate the effect of multiple once daily doses of dexlansoprazole modified release (MR) (TAK-390 MR) 90 mg on the pharmacokinetics of theophylline following a single intravenous (IV) dose of aminophylline.			
Methodology: This was a Phase 1, double-blind, placebo-controlled, two-way crossover study. Subjects who met the study eligibility criteria were randomly assigned in a 1:1 ratio to 2 treatment sequence groups. Subjects received both regimens in a crossover fashion as outlined below:			
Sequence	No. of Subjects	Regimens	
		Period 1	Period 2
1	10	Regimen A	Regimen B
2	10	Regimen B	Regimen A
Regimen A = Dexlansoprazole MR 90 mg once daily for 9 consecutive days + a single 400-mg IV dose of aminophylline administered as a 30-minute IV infusion on Day 8.			
Regimen B = Placebo for dexlansoprazole MR once daily for 9 consecutive days + a single 400-mg IV dose of aminophylline administered as a 30-minute IV infusion on Day 8.			
For both periods, confinement began on Day -1 and ended on Day 10 after all procedures had been completed. On Days 1 to 9 in each period, subjects received dexlansoprazole MR 90 mg or placebo for dexlansoprazole MR (hereinafter referred to as placebo) at approximately 0800 hours following a 10-hour fast. On Day 8 of each period, subjects were co-administered a single 400-mg IV dose of aminophylline together with dexlansoprazole MR 90 mg or placebo. One hour after study drug administration on Days 1 through 9, subjects received a standardized breakfast. All subjects received the same standardized meals in both dosing periods. There was a washout interval of at least 10 days between the last dose of study drug in Period 1 and the first dose of study drug in Period 2. On completion of the study, each subject had received both regimens.			
Blood samples were collected to determine the plasma concentration of theophylline on Day 8 of each period until 48 hours postdose. A limited number of blood samples for the determination of plasma concentrations of dexlansoprazole were collected on Day 8 of each period.			
Safety was monitored through adverse event (AE) reports, concomitant medication usage, 12-lead electrocardiograms (ECGs), physical examinations, vital sign assessments, and laboratory evaluations. In addition, subjects were also monitored for theophylline toxicity on Day 8 of each period and underwent cardiac telemetry monitoring starting 30 minutes before the start of the aminophylline IV infusion.			
Number of Subjects (Planned and Analyzed): 20 planned; 20 enrolled; 19 included in pharmacokinetic (PK) analysis; 20 included in safety analysis; Gender: 8 males and 12 females; Race: 20 white; Ethnicity: 20 Hispanic or Latino; Mean age ± standard deviation (SD): 36.8 ± 9.69 years.			
Diagnosis and Main Criteria for Inclusion: Healthy male or female subjects aged 18 to 55 years, inclusive, at Day 1 of Period 1.			

Duration of Treatment: Dexamproprazole MR 90 mg or placebo capsule was administered to subjects on Days 1 to 9 of each of the 2 treatment periods. A single 400-mg IV dose of aminophylline was administered as a 30-minute IV infusion on Day 8 of each of the 2 treatment periods. There was at least 10 days of washout between the last dose of Period 1 and the first dose of Period 2.

Test Product, Dose and Mode of Administration, and Lot Numbers:

Study Drug	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Drug Product Lot Number
Dexamproprazole MR	One 90-mg capsule	90 mg once daily	Oral	Takeda Pharmaceutical Company Limited	Z540S042

Reference Therapy, Dose and Mode of Administration, and Lot Numbers:

Study Drug	Product Dosage Strength	Study Dose	Mode of Administration	Manufacturer	Drug Product Lot Number
Placebo for dexamproprazole MR	One capsule	NA once daily	Oral	Takeda Pharmaceutical Company Limited	Z540T022
Aminophylline	20 mL ampule containing 500 mg aminophylline dihydrate (25 mg/mL aminophylline dehydrate IV solution)	400 mg (315.2 mg anhydrous theophylline)	IV	Hospira	32-686-DK

NA = not applicable

Criteria for Evaluation:

Pharmacokinetics:

Pharmacokinetic parameters for theophylline in plasma were estimated using standard noncompartmental methods. The pharmacokinetic parameters included: the observed maximum plasma concentration (C_{max}), the time to reach the observed maximum concentration (t_{max}), the last measurable plasma concentration (C_t), theophylline concentration at 48 hours postdose (C_{48}), the time to reach the observed last measurable concentration (t_{last}), the apparent terminal elimination rate constant (λ_z), the half-life of the apparent terminal elimination-phase half-life ($t_{1/2}$), and area under the plasma concentration time-curve (AUC) from time zero to the last measurable concentration (AUC_t), and from zero to infinity (AUC_{∞}). In addition, the total body clearance (CL) and volume of distribution (V_z) for theophylline were estimated.

Safety:

Subject safety was evaluated based on reported AEs, physical examinations, vital signs, cardiac telemetry on Day 8, ECGs, and safety laboratory tests. Standard safety laboratory assessments (including chemistry, hematology, and urinalysis) were conducted for this study and drawn at the Screening Visit and Days -1 and 10 of each of the 2 periods.

Statistical Methods:

Pharmacokinetics:

Analyses of variance (ANOVAs) were performed on the theophylline t_{max} and t_{last} and the natural logarithms of C_{max} , C_{48} , AUC_t , and AUC_{∞} , with factors for sequence, subjects nested within sequence, period, and regimen. The factor of subjects nested within sequence will be considered random, and all other factors will be fixed. The effect of

dexlansoprazole MR was assessed via 90% confidence intervals for the ratio of dexlansoprazole MR plus theophylline to placebo plus theophylline central values for theophylline C_{max} and AUCs. A conclusion of no effect of dexlansoprazole MR on the pharmacokinetics of theophylline was to be made if the 90% confidence intervals were within (0.80, 1.25) for theophylline C_{max} and AUCs.

In order to further assess the potential induction of dexlansoprazole MR on hepatic cytochrome P450 (CYP) 1A2 activity, C_{48} was also analyzed using above ANOVA model. During the analysis, if the reported concentration value was below lower limit of quantitation (LLOQ), the value of LLOQ/2 was used instead. A conclusion of no effect of dexlansoprazole MR on C_{48} was made if the 90% confidence intervals of the central value ratio of C_{48} of 2 regimens were completely contained within the range of 0.80 to 1.25.

Safety:

The incidence of AEs was tabulated using Medical Dictionary of Regulatory Activities (MedDRA) classifications and terms. Laboratory parameters, ECGs, and vital signs were summarized descriptively for each regimen. Potentially concerning laboratory values and vital signs results were listed.

Summary and Conclusions:

Pharmacokinetic Results:

Noncompartmental pharmacokinetic parameter estimates for theophylline following a single 400-mg IV dose of aminophylline dihydrate (315.2 mg anhydrous theophylline) are summarized below:

Treatment	t_{max} (hr)	C_{max} ($\mu\text{g/mL}$)	C_{48} ($\mu\text{g/mL}$)	AUC_t ($\text{hr}\cdot\mu\text{g/mL}$)	AUC_{∞} ($\text{hr}\cdot\mu\text{g/mL}$)	$t_{1/2}$ (hr) ^a	CL (L/h)	V_z (L)
Regimen A								
N	19	19	19	19	19	19	19	19
Mean	0.692	12.35	229.74	122.3	126.5	8.48 (8.20)	2.62	31.25
%CV	27	25	63	23	23	19	22	18
Regimen B								
N	19	19	19	19	19	19	19	19
Mean	0.649	11.66	275.32	126.6	131.8	9.26 (8.94)	2.51	32.89
%CV	23	22	67	22	23	19	23	21

^a Arithmetic mean (harmonic mean).

%CV = percentage of coefficient of variation.

Regimen A = Dexlansoprazole MR 90 mg once daily for 9 consecutive days + a single 400-mg IV dose of aminophylline administered as a 30-minute IV infusion on Day 8.

Regimen B = Placebo for dexlansoprazole MR once daily for 9 consecutive days + a single 400-mg IV dose of aminophylline administered as a 30-minute IV infusion on Day 8.

Following administration of a single 400-mg dose of aminophylline as an IV infusion over 30 minutes, the mean plasma concentration-time profiles of theophylline from Regimens A and B were nearly superimposable. Mean C_{max} , C_{48} , AUC_{∞} , and $t_{1/2}$ values for theophylline in the Regimens A and B were similar. In addition, the estimated CL, V_z , and $t_{1/2}$ values for theophylline did not appear to be different between Regimens A and B.

The statistical assessment of the effect of dexlansoprazole on the pharmacokinetics of theophylline performed via 90% confidence intervals for the ratio of central values. The ratios of central values and their 90% confidence intervals for C_{max} , AUC_t , and AUC_{∞} values are summarized in the following table.

Parameter	Regimen A vs Regimen B	
	Point Estimate	90% Confidence Interval
C_{max}	1.05	(0.9650 – 1.1336)
AUC_t	0.96	(0.9318 – 0.9975)
AUC_{∞}	0.96	(0.9284 – 0.9917)
<p>Regimen A = Dexlansoprazole MR 90 mg once daily for 9 consecutive days + a single 400-mg IV dose of aminophylline administered as a 30-minute IV infusion on Day 8.</p> <p>Regimen B = Placebo for dexlansoprazole MR once daily for 9 consecutive days + a single 400-mg IV dose of aminophylline administered as a 30-minute IV infusion on Day 8.</p> <p>The 90% confidence intervals for the ratio of the central values between Regimens A and B were within the bioequivalence range of 0.80 to 1.25 for theophylline C_{max}, AUC_t, and AUC_{∞} values. The ratio of the central value for C_{4S}, and its 90% confidence intervals were 0.8695 and 0.7188 to 1.0519. Although the 90% confidence interval for C_{4S} fell just below the 0.8 boundary, the overall systemic exposure of theophylline was not affected.</p> <p>A limited number plasma samples for the quantification of dexlansoprazole were obtained in this study. All subjects received the oral doses of placebo or dexlansoprazole MR according to the sequence specified in the randomization schedule.</p> <p>Safety Results:</p> <p>More subjects experienced AEs while receiving placebo plus aminophylline (Regimen B) than while receiving dexlansoprazole MR plus aminophylline (Regimen A) and there were no trends observed in AEs associated with the administration of dexlansoprazole MR in this study. After the first dose of study drug, all occurrences of Tachycardia (MedDRA Preferred Term [PT]), Dizziness (MedDRA PT), and 8 of the 9 occurrences of Palpitations (MedDRA PT), occurred on Day 8 of Regimen A or B, either during the infusion of the dose of aminophylline or within 30 minutes after the completion of the infusion of the dose of aminophylline. The AEs of Palpitations, Tachycardia, and Dizziness are consistent with AEs commonly seen with administration of aminophylline alone. No deaths or other serious AEs occurred, and no subject prematurely discontinued the study due to an AE. No consistent, clinically important changes in laboratory test results, vital signs, physical examinations, or ECGs were observed.</p> <p>Conclusions:</p> <p>Once daily oral doses of dexlansoprazole MR 90 mg in healthy subjects had no effect on the pharmacokinetics of theophylline following administration of a single 400-mg IV dose of aminophylline. These results indicate that dexlansoprazole does not affect hepatic CYP1A2 activity in humans and, therefore, will not alter the metabolism of other drugs metabolized by this enzyme. No dose adjustment is required for theophylline when administered concomitantly with dexlansoprazole MR.</p> <p>In this study, no safety concerns were associated with administration of dexlansoprazole MR alone or with a single 400-mg IV dose of aminophylline in healthy subjects.</p>		

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Title of Study: A Phase I, Randomized, Double-Blind, Placebo-Controlled, Ascending Single Dose Study of the Safety, Tolerability and Pharmacokinetics of TAK-390MR in Healthy Male Subjects	
Name of Sponsor: Takeda Pharmaceutical Company Ltd. (TPC)	
Name of Active Ingredient: Dexlansoprazole (INN)	
Name of Finished Product: Not applicable	
Investigator(s): (b) (4)	Study Center(s): (b) (4)
Publication (reference):	
Study Period (years): 24 December, 2005 (date first subject gave his consent) to 17 April, 2006 (date last subject underwent final examination)	Phase of Development: Phase 1
OBJECTIVES	
Primary: The primary objective was to examine the single oral dose safety and pharmacokinetics of TAK-390MR in healthy Japanese adult male subjects with a double-blind, placebo-controlled design.	
Secondary: The secondary objective was to evaluate the effects of food on the single oral dose safety and pharmacokinetics of TAK-390MR in each subject using a 2-period crossover method.	
METHODOLOGY	
This was a single-center, randomized, double-blind, single-dose, placebo-controlled study consisting of Steps 1 through 5 designed with an ascending dose method and Step 6 designed with a 2-period crossover method. In Steps 1 through 5, 80 subjects including 40 EMs (Extensive Metabolizers) and 40 PMs (Poor Metabolizers), received a single oral dose of TAK-390MR at 15 mg, 30 mg, 60 mg, 90 mg, or 120 mg, or placebo with 200 mL of water under a fasted state to evaluate the safety and pharmacokinetic profiles. In Step 6, 12 EMs received a single oral dose of TAK-390MR 60 mg or placebo with 200 mL of water both in fed and fasted states to evaluate the food effects on the safety and pharmacokinetics. Safety was monitored through physical examination, vital sign assessments, 12-lead ECGs (ECGs), and laboratory tests. Pharmacokinetics was evaluated with plasma and urinary drug concentrations.	
Number of Subjects:	
Planned: 92 subjects	
Analyzed: Safety Population — 92 subjects; PK Population — 92 subjects;	
Diagnosis and Main Criteria for Inclusion:	
To qualify for study participation, subjects must have been subjects who meet all of the following criteria:	
<ol style="list-style-type: none"> 1. subjects between the ages of 20 and 35 when giving their informed consent 2. subjects having either [*1/*1, *1/*2, *1/*3] (EMs) or [*2/*2, *2/*3, *3/*3] (PMs) of CYP2C19 	

<p>genotypes</p> <ol style="list-style-type: none"> 3. subjects weighing at least 50 kg at screening 4. subjects having a BMI within the range of 18.5 and 24.9 at screening 5. subjects judged to be eligible for the study by the investigator or sub investigator on the basis of screening results and pre-dose findings obtained with physical examination, vital sign assessments, ECGs, and laboratory tests 6. subjects having negative HBc, HCV antibody, HIV antibody, and serological reaction with syphilis 7. subjects volunteering to participate in this study who are able to give their written informed consent 														
<p>Test Product, Dose and Mode of Administration/Lot Number:</p> <table border="0" style="width: 100%;"> <thead> <tr> <th></th> <th style="text-align: right;"><u>Batch/Lot Number</u></th> </tr> </thead> <tbody> <tr> <td>TAK-390MR 15 mg capsule, 1 capsule orally dosed under fasted states (Step 1)</td> <td style="text-align: right;">DB540Y011</td> </tr> <tr> <td>TAK-390MR 30 mg capsule, 1 capsule orally dosed under fasted states (Step 2)</td> <td style="text-align: right;">DB540a012</td> </tr> <tr> <td>TAK-390MR 60 mg capsule, 1 capsule orally dosed under fasted states (Step 3)</td> <td style="text-align: right;">DB540e011</td> </tr> <tr> <td>TAK-390MR 45 mg capsule, 2 capsule orally dosed under fasted states (Step 4)</td> <td style="text-align: right;">DB540c011</td> </tr> <tr> <td>TAK-390MR 60 mg capsule, 2 capsule orally dosed under fasted states (Step 5)</td> <td style="text-align: right;">DB540e012</td> </tr> <tr> <td>TAK-390MR 60 mg capsule, 1 capsule orally dosed under fed and fasted states (Step 6)</td> <td style="text-align: right;">DB540e011</td> </tr> </tbody> </table>		<u>Batch/Lot Number</u>	TAK-390MR 15 mg capsule, 1 capsule orally dosed under fasted states (Step 1)	DB540Y011	TAK-390MR 30 mg capsule, 1 capsule orally dosed under fasted states (Step 2)	DB540a012	TAK-390MR 60 mg capsule, 1 capsule orally dosed under fasted states (Step 3)	DB540e011	TAK-390MR 45 mg capsule, 2 capsule orally dosed under fasted states (Step 4)	DB540c011	TAK-390MR 60 mg capsule, 2 capsule orally dosed under fasted states (Step 5)	DB540e012	TAK-390MR 60 mg capsule, 1 capsule orally dosed under fed and fasted states (Step 6)	DB540e011
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<p>Duration of Treatment:</p> <p>Each subject received a single oral dose of a study drug in Steps 1 through 5 and a double oral dose at a 1-week interval in Step 6.</p>														
<p>Reference Therapy, Dose and Mode of Administration, Batch Number:</p> <p>TAK-390MR placebo capsule was administered with the same condition as the corresponding active capsule.</p>														
<p>Criteria for Evaluation:</p> <p>Efficacy was not assessed in this study.</p> <p><u>Pharmacokinetics:</u></p> <p>Plasma concentrations of TAK-390, T-168391 (S-enantiomer of lansoprazole), and main metabolites (M-VI, M-VII), and urinary excretion rates of TAK-390 (including T-168391) and main metabolites (M-VI, M-VII) were assessed.</p>														
<p>Safety:</p> <p>Safety was monitored by the assessment of AEs, clinical laboratory variables, vital signs, body weight, and ECG findings.</p>														
<p>Statistical Methods:</p> <p><u>Pharmacokinetics:</u></p> <p>Pharmacokinetic parameters of TAK-390, T-168391, and main metabolites in plasma were estimated using standard noncompartmental methods. The pharmacokinetic parameters included the area under the plasma concentration-time curve from time zero to 48 hours (AUC_{0-48}), from time zero to the time of the last measurable concentration (AUC_{last}), and from time zero to infinity (AUC_{inf}); the area under the primary moment-time curve from time zero to the time of the last measurable concentration ($AUMC_{last}$) and from time zero to infinity ($AUMC_{inf}$); the mean residence time from time zero to the last measurable concentration (MRT_{last}) and from time zero to infinity (MRT_{inf}); the maximum plasma concentration (C_{max}), the time to reach the maximum plasma concentration (t_{max}), the terminal elimination rate constant (kel), the terminal elimination half-life ($t_{1/2}$), and the apparent total body clearance (CL/F). The fractional and accumulative urinary excretion rates of TAK-390 (including T-168391), main metabolites, and a total of them were estimated.</p>														

Safety

All subjects receiving at least one dose of the study drug were included in the safety analysis. Adverse events were summarized for each step and metabolizer (EM or PM). Baseline and post-dose values and mean changes from baseline to post-dose were summarized by step and metabolizer for vital signs, body weight, ECG findings, and clinical laboratory variables.

SUMMARY OF RESULTS

Subject Disposition:

A total of 92 male subjects (mean age of 21.9), were randomized in the study from the 208 subjects who were screened. 92 subjects completed the study. No subjects discontinued the study and no data were excluded from the analysis populations.

Mean age, height, weight, and BMI of the subjects were similar among the treatment groups.

Pharmacokinetic Results:

TAK-390 was gradually absorbed in two phases following a single oral dose of TAK-390MR ranging from 15 mg to 120 mg and almost disappeared from circulation by 48 hours post administration. No plasma concentration of T-168391 was detected. The pharmacokinetic parameters of TAK-390 are summarized in the following table:

Doses	AUC ₀₋₄₈ (ng·hr/mL)		AUC _{last} (ng·hr/mL)		MRT _{last} (hr)		C _{max-1} (ng/mL)		C _{max-2} (ng/mL)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
15 mg	3908.3	3031.91	3659.4	2751.11	7.374	1.6908	268.5	67.02	444.5	299.24
30 mg	9817.8	8721.50	9459.4	8496.59	8.634	2.6845	518.8	191.74	927.7	627.24
60 mg	18302.9	14009.27	17910.6	13779.95	8.455	2.3396	987.4	753.83	1656.5	1298.42
90 mg	24712.0	16827.16	24185.0	16296.72	8.461	2.5740	1330.3	699.01	2389.1	1729.89
120 mg	35010.2	24256.32	34944.8	24317.62	8.768	3.0425	2725.8	615.06	3161.8	2126.75

Doses	t _{max-1} (hr)		t _{max-2} (hr)		kel (hr ⁻¹)		t _{1/2} (hr)		CL/F (L/hr)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
15 mg	2.083	0.7638	6.250	1.7123	0.2900	0.15922	2.9794	1.30335	7.45	6.217
30 mg	2.417	1.0624	6.083	1.6765	0.3022	0.21778	3.4500	1.95219	7.97	7.686
60 mg	1.958	1.2515	5.818	1.6624	0.3380	0.23494	3.1638	1.83405	7.23	6.354
90 mg	2.000	1.0445	5.500	1.5076	0.2998	0.20318	3.2862	1.73542	6.78	5.810
120 mg	1.708	0.7217	7.083	1.5643	0.2712	0.17243	3.7345	2.16748	6.19	4.868

Mean t_{1/2} ranged from 2.98 to 3.73 over the doses between 15 and 120 mg. Mean C_{max} and mean AUC increased dose-dependently while MRT, mean kel, and mean CL/F were relatively stable over the doses between 15 and 120 mg. The dose proportionality of the AUC₀₋₄₈, AUC_{last}, AUC_{inf}, and C_{max} of TAK-390 was evaluated with power model and linear regression analyses. The results demonstrated that the AUC and C_{max} of TAK-390 increased linearly with the dose escalation of TAK-390MR.

Main metabolites, M-VI and M-VII, appeared in circulation slightly later than TAK-390 and plasma concentrations of them, especially M-VI, gradually increased in two phases in the same way as TAK-390. M-VI reached peak plasma concentrations approximately by 6 hours after TAK-390MR administration and disappeared from circulation by 48 hours. The plasma M-VII concentrations in several subjects were less than a LLOQ (5 ng/mL) at all time points of measurement. Mean C_{max} and mean AUC of two metabolites increased nearly dose-dependently. MRT and mean kel of M-VI were relatively stable over the doses between 15 and 120 mg.

Mean cumulative urinary excretion rates (% of doses) of TAK-390 until 48 hours after TAK-390MR administration was less than 0.1 %, being lower than that of M-VI (<0.4 %). No M-VII was detected even in the urine samples of the subjects who were administered the highest dose (120 mg).

The absorption of TAK-390 tended to be delayed by food. However, mean C_{max} and AUC₀₋₄₈ of TAK-390 following the administration of TAK-390MR under fed condition were approximately 145.2 % and 116.5% for those under fasting condition, respectively, and MRT was slightly prolonged by food. Mean t_{1/2} and kel

<p>were similar between fasting and fed dose conditions. TAK-390 completely disappeared from circulation by 24 hours post administration either under fasting or fed condition. The results of ANOVA and confidence interval estimation for the food effect and the period effect on AUC_{0-48}, AUC_{last}, AUC_{inf}, and C_{max} of TAK-390 demonstrated that the AUC was not almost influenced by food and that the C_{max} increased with food.</p> <p>The t_{max} of TAK-390 was not significantly different between EMs and PMs while the $t_{1/2}$ in PMs was significantly longer than in EMs. The AUC of TAK-390 in PMs was approximately 5 times of that in EMs.</p>
<p>Safety Results:</p> <p>Two AEs were reported in one subject receiving an oral dose of TAK-390MR at 60 mg under fasting condition (Step 6). These were mild increases in ALT and AST, which were considered not to be related to the study drug for the reason that these were temporary changes due to insufficient exercise during the study and were not observed in him at the first dose in Period 1 of Step 6. No other AEs were observed during the study.</p>
<p>CONCLUSIONS:</p> <p>Because the C_{max} and AUC of TAK-390 increased linearly with the dose escalation, the pharmacokinetic profile of TAK-390MR was considered to be a linearity between 15 mg and 120 mg. The absorption of TAK-390 tended to be delayed by food while the AUC was not almost influenced.</p> <p>The single oral dose of TAK-390MR was well tolerated up to 120 mg in healthy Japanese adult males.</p>
<p>Date of Report: 17 October 2007</p>

In-vitro metabolism studies

XT053037

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Abstract

This study was designed to compare racemic lansoprazole (lansoprazole) with its individual enantiomers, dexlansoprazole (*R*-lansoprazole or TAK-390) and *S*-lansoprazole (T-168391), as inducers of microsomal cytochrome P450 (CYP) enzymes in primary cultures of human hepatocytes. Cultured human hepatocytes from three separate donors were treated once daily for three consecutive days with dexlansoprazole, *S*-lansoprazole or lansoprazole at 1, 10, 25, or 100 μM . Cultures treated with dimethylsulfoxide (0.1% DMSO, w/v) served as negative controls, whereas cultures treated with omeprazole (100 μM), phenobarbital (750 μM), or rifampin (10 μM) served as positive controls. After the treatment period, microsomes were isolated and analyzed for activities known to be specific for CYP1A2, 2B6, 2C9, 2C19 and 3A4 (namely phenacetin *O*-dealkylation, bupropion hydroxylation, diclofenac 4'-hydroxylation, *S*-mephenytoin 4'-hydroxylation and testosterone 6 β -hydroxylation, respectively).

Treatment of cultured human hepatocytes with the prototypical CYP inducers caused anticipated increases in CYP activities. On average, treatment with omeprazole caused a 34.3-fold increase in CYP1A2; phenobarbital caused an 11.4-fold increase in CYP2B6, and rifampin caused a 2.17-fold increase in CYP2C9, a 5.27-fold increase in CYP2C19 and a 5.71-fold increase in CYP3A4.

Daily microscopic examination of the first hepatocyte culture (H655) treated with the highest concentration (100 μM) of dexlansoprazole, *S*-lansoprazole or lansoprazole revealed evidence of cell toxicity in all three cases. Therefore, in the second and third cultures (H656 and H658), the range of concentrations of each test article was changed from 1, 10 and 100 μM to 1, 10 and 25 μM , none of which caused any discernible signs of cell toxicity.

In all three preparations of human hepatocytes, dexlansoprazole, *S*-lansoprazole or lansoprazole all caused concentration-dependent increases in CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4 activity. At 10 μM , the magnitude of CYP induction was less than 40% of the appropriate positive control, as summarized in the following table.

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CYP induction in human hepatocytes treated with 10 and 25 μ M dexlansoprazole, S-lansoprazole or lansoprazole as a percent of positive control

The two values are the percent of positive control for two different concentrations (10 and 25 μ M) of each test article. The positive controls are shown in parentheses under the relevant CYP enzyme.

Test article	CYP1A2 (omeprazole)	CYP2B6 (phenobarbital)	CYP2C9 (rifampin)	CYP2C19 (rifampin)	CYP3A4 (rifampin)
Dexlansoprazole	12.4% & 31.8%	10.8% & 24.5%	29.2% & 62.5%	4.45% & 9.27%	28.0% & 34.0%
S-Lansoprazole	9.50% & 23.2%	6.94% & 25.4%	17.9% & 41.9%	0.09% & 9.15%	32.4% & 46.0%
Lansoprazole	10.5% & 26.7%	9.31% & 20.9%	23.4% & 54.5%	4.41% & 12.3%	31.1% & 41.3%

At 25 μ M, the magnitude of CYP induction by all three test articles was less than 40% of the appropriate positive control in the case of CYP1A2, 2B6 and 2C19 (see above table). At 25 μ M, dexlansoprazole, S-lansoprazole and lansoprazole were 62.5, 41.9 and 54.5% as effective as rifampin at inducing CYP2C9, and 34.0, 46.0 and 41.3% as effective as rifampin at inducing CYP3A4, respectively.

Treatment of human preparation, H655, with 100 μ M dexlansoprazole, S-lansoprazole or lansoprazole caused a concentration-dependent increase in CYP1A2, CYP2B6, and CYP2C19 activity, even with the observed toxicity. However, treatment with 100 μ M dexlansoprazole, S-lansoprazole or lansoprazole caused a lower fold-increase than that observed with treatment at 25 μ M dexlansoprazole, S-lansoprazole or lansoprazole in CYP2C9 and CYP3A4, with the exception of dexlansoprazole and CYP2C9 activity, in which there was a concentration-dependent increase. The cause of these lowered activities is unknown, but was most likely a result of the toxicity that was observed in this human preparation.

These results establish that the individual enantiomers of lansoprazole, like the racemic mixture, can induce multiple CYP enzymes in human hepatocytes, and do so over the same concentration range. At 25 μ M, dexlansoprazole, S-lansoprazole and racemic lansoprazole induced CYP2C9 and CYP3A4 from 34.0 to 62.5% of the positive control rifampin. However, at 10 μ M, none of the test articles induced any of the CYP enzymes more than 40% of the appropriate positive control. In terms of efficacy (magnitude of CYP induction) and potency (effective concentrations), there were no notable differences between dexlansoprazole and S-lansoprazole, or between either enantiomer and the racemic mixture. The results suggest that, at comparable plasma levels, dexlansoprazole and S-lansoprazole administered as individual enantiomers would cause the same degree of enzyme induction as that observed clinically with racemic lansoprazole.

At typically observed maximum dexlansoprazole concentrations of 1 to 6 μ M following oral administration of 30 mg to 90 mg modified-release formulation of dexlansoprazole, the enzyme induction effect of dexlansoprazole observed in this *in vitro* study may not be clinically relevant.

Study XT054023

1. Abstract

Previous studies indicate that the proton pump inhibitor lansoprazole, a racemic mixture, is metabolized by CYP2C19 and CYP3A4 to two major metabolites, 5-hydroxylansoprazole and lansoprazole sulfone in human. The aim of this study was to compare racemic lansoprazole with its two enantiomers, dexlansoprazole [(*R*)-enantiomer of lansoprazole or TAK-390] and (*S*)-lansoprazole [(*S*)-enantiomer of lansoprazole or T-168391] in terms of (1) their metabolism by recombinant human CYP2C19 and CYP3A4 and (2) their metabolism by human liver microsomes from donors genotyped as CYP2C19 extensive metabolizers (EMs) or poor metabolizers (PMs).

With all three substrates, recombinant CYP2C19 catalyzed only the 5-hydroxylation reaction, and the *in vitro* intrinsic clearance (Cl_{int}) by this pathway was assessed from measurements of V_{max}/K_m (the Michaelis Menten kinetic constants). Compared with the intrinsic clearance of racemic lansoprazole ($Cl_{int} = 6.77 \mu\text{L}/\text{pmol P450}/\text{min}$), the *in vitro* intrinsic clearance by recombinant CYP2C19 was slower in the case of dexlansoprazole ($Cl_{int} = 4.96 \mu\text{L}/\text{pmol P450}/\text{min}$) and slightly faster in the case of (*S*)-lansoprazole ($Cl_{int} = 7.01 \mu\text{L}/\text{pmol P450}/\text{min}$). Despite their similar intrinsic clearance values (4.96 *versus* 7.01), dexlansoprazole and (*S*)-lansoprazole interacted quite differently with CYP2C19: dexlansoprazole was a relatively low affinity, high capacity substrate ($K_m = 4.11 \mu\text{M}$, $V_{max} = 20.4 \text{ pmol}/\text{min}/\text{pmol P450}$) whereas (*S*)-lansoprazole was high affinity, low capacity substrate ($K_m = 0.278 \mu\text{M}$, $V_{max} = 1.95 \text{ pmol}/\text{min}/\text{pmol P450}$).

Recombinant CYP3A4 converted all three substrates to both 5-hydroxylansoprazole and lansoprazole sulfone. The latter reaction predominated in a substrate-dependent manner inasmuch as the ratio of sulfoxidation to 5-hydroxylation (based on *in vitro* intrinsic clearance) was 8.1 for racemic lansoprazole, 1.81 for dexlansoprazole and 17.4 for (*S*)-lansoprazole. Based on the combined *in vitro* intrinsic clearance rates for both metabolites, (*R*)-lansoprazole ($Cl_{int} = 0.374 \mu\text{L}/\text{pmol P450}/\text{min}$) was metabolized by CYP3A4 at only 41% of the rate of racemic

lansoprazole ($Cl_{int} = 0.919 \mu\text{L}/\text{pmol P450}/\text{min}$), whereas (*S*)-lansoprazole ($Cl_{int} = 1.27 \mu\text{L}/\text{pmol P450}/\text{min}$) was metabolized 38% faster than the racemic drug. The studies with recombinant CYP enzymes suggest that (*S*)-lansoprazole is cleared faster than dexlansoprazole by both CYP2C19 and CYP3A4 (1.4- and 3.4-fold faster, respectively).

Human liver microsomes preferentially converted all three substrates to 5-hydroxylansoprazole over lansoprazole sulfone. In each case, formation of 5-hydroxylansoprazole correlated well with CYP2C19 activity, whereas formation of lansoprazole sulfone correlated well with CYP3A4 activity, based on studies with two samples of human liver microsomes from CYP2C19 EMs and two samples from CYP2C19 PMs (plus pooled human liver microsomes, which supported an intermediate rate of metabolite formation from all three substrates). At concentrations tested (0.5 μM and 5 μM), (*S*)-lansoprazole was metabolized at about the same rate as racemic lansoprazole in the EM and PM samples, whereas dexlansoprazole was metabolized at a slower rate. Based on the absolute and relative rates of formation of 5-hydroxylansoprazole and lansoprazole sulfone, the relatively slow rate of metabolism of dexlansoprazole by human liver microsomes can be ascribed to a slightly slower rate of metabolism by CYP2C19 and a markedly slower rate of metabolism by CYP3A4.

These *in vitro* results suggest that the clearance of dexlansoprazole would be lower *in vivo* and, hence, exposure correspondingly higher than (*S*)-lansoprazole or racemic lansoprazole. Compared with the dexlansoprazole, the (*S*)-enantiomer was metabolized faster by both CYP3A4 and, to a lesser extent, by CYP2C19; hence, (*S*)-lansoprazole was metabolized faster than dexlansoprazole by liver microsomes from both CYP2C19 EMs and PMs.

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Food Effect Study T-P104-069

Study Title: A Phase 1, Randomized, Open-Label, Single-Dose, Four-Period Crossover Study Comparing the Pharmacokinetics of a 90mg Modified-Release TAK-390 Formulation Administered Orally Under Fed and Fasting Conditions in Healthy Subjects

Study Site: Clinical Site & Analytical Site: (b) (4)

Objectives:

The objectives of this study were to compare the effect of feeding conditions of the pharmacokinetics of a single 90mg dose of TAK-390MR and to evaluate the safety of the test product.

Study Design:

This was a Phase 1, open-label, single-center, single-dose, 4-sequence, 4-period crossover study in which volunteers received one 90mg capsule under each of 4 different feeding conditions. Volunteers were randomly assigned to the sequence in which they received each regimen. A minimum of 5 days separated each period. Blood sampling for PK analysis occurred up to 24 hours post-dose.

TAK-390MR Capsule Granules by Type, pH of Release, and Proportion of total Dose:

Granule Type	pH of Release	Proportion of TAK-390 Dose
Type 1 (b) (60mg & 90mg strength) (4) (30mg strength)	5.5	25%
Type 2 (b) (all strengths)	6.75	75%

Feeding Conditions of the Four Regimens to which Volunteers were Randomly Assigned

Regimen	Feeding Conditions
A	After fasting for at least 10 hours, the subject received the 90-mg dose of TAK-390MR and continued to fast for an additional 4 hours before receiving a standard lunch.
B	After fasting for at least 9.5 hours, the subject had a standardized high-fat breakfast that was consumed within 25 minutes, and received the 90-mg dose of TAK-390MR 30 minutes after starting to eat the breakfast.
C	After fasting for at least 10 hours, the subject received the 90-mg dose of TAK-390MR and consumed a standard high-fat breakfast that started 30 minutes after dosing.
D	After fasting for at least 10 hours, the subject received the 90-mg dose of TAK-390MR and consumed a standard high-fat breakfast that started 1 hour after dosing.

Volunteers receiving Regimens B, C, & D were served the following standardized high-fat breakfast:

- 2 Eggs fried in butter
- 2 Strips of bacon
- 2 Slices of toast with butter
- 4 Ounces of hash brown potatoes
- 8 Ounces of whole milk

Sequences to which Volunteers were Randomly Assigned

Sequence	Number of Subjects	Period 1	Period 2	Period 3	Period 4
1	7	Regimen A	Regimen D	Regimen B	Regimen C
2	7	Regimen B	Regimen A	Regimen C	Regimen D
3	7	Regimen C	Regimen B	Regimen D	Regimen A
4	7	Regimen D	Regimen C	Regimen A	Regimen B

Key Inclusion Criteria

Healthy males and non-pregnant females ages 19-55 years of age with a BMI 18-32 kg/m² were eligible for the study.

Key Exclusion Criteria

Subjects with a positive *H. pylori* test, current or recent GI disease (within past 6 months), as well as a history of surgical intervention that may result in a change in drug absorption were excluded. The use of any renal or hepatic clearance-altering agents within the past 30 days was cause for exclusion.

Study Population:

Investigators enrolled 28 adults, 14 males and 14 females, in this food-effect study. Of the total, 25 (89%) received all four doses of TAK-390MR. Three volunteers discontinued the study secondary to abnormal laboratory values considered unrelated to the study drug.

Study Population Demographics

Demographic Variable	All Subjects (N=28)
Gender n (%)	
Male	14 (50.0%)
Female	14 (50.0%)
Race n (%)	
Black	3 (10.7%)
Caucasian	23 (82.1%)
Hispanic	2 (7.1%)
Age (years)	
Mean ± SD	32.5 ± 11.27
Median	29.5
min-max	19 - 55
Weight (pounds)	
Mean ± SD	168.4 ± 33.50
Median	176.5
min-max	100 - 228
Height (inches)	
Mean ± SD	66.7 ± 3.94
Median	67.0
min-max	58 - 73

Pharmacokinetic Measurement:

Thirty-one blood samples were drawn over the 24-hour study period. Samples were drawn most frequently in the first 10 hours in order to accurately characterize the absorption features of the two different types of granules present.

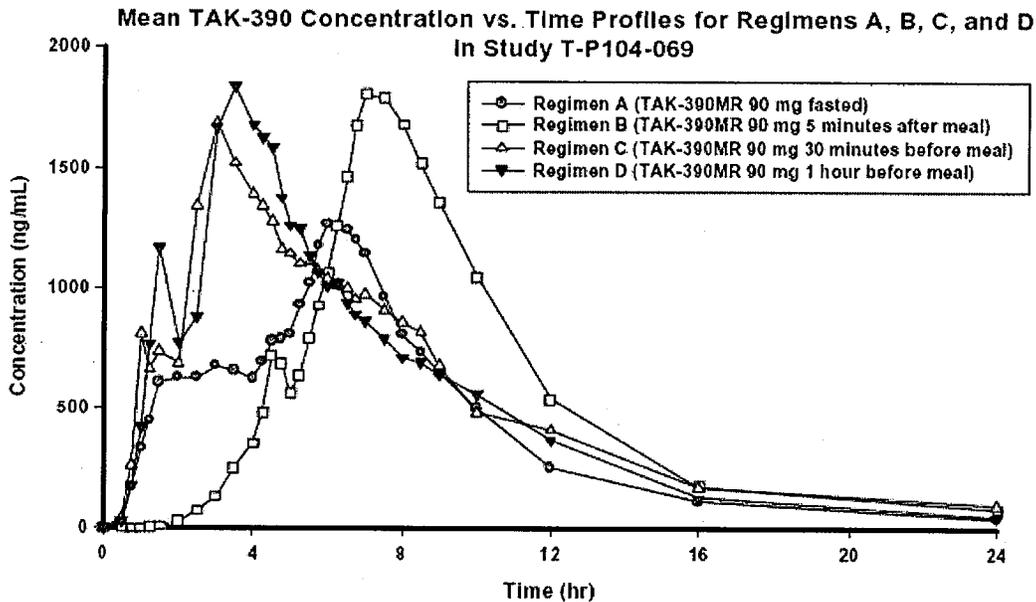
Bioanalytical Analysis:

TAK-390 levels were measured by LC/MS/MS.

Analyte	Method	LLOQ	ULOQ	QC precision	QC accuracy
TAK-390	LC/MS/MS	5.00 ng/mL	1200 ng/mL	2.7% – 4.8%	1.2 – 12.1%

Pharmacokinetic Results:

Mean Plasma Concentration-Time Profiles of TAK-390 Following Oral Administration of 90mg under Fasted or Various Fed Conditions



Plasma PK parameter estimates for TAK-390 under fasted or various fed conditions.

Regimen	Measure	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC (ng·h/mL)	$t_{1/2}$ ^a (h)
A (90 mg TAK-390MR fasted)	N	27	27	27	27	27
	Mean	4.66	1811.85	9254.84	9665.43	1.54
	SD	2.41	903.19	8213.87	9773.30	-
	CV%	52	50	89	101	75
B (90 mg TAK-390MR 30 minutes after the start of a meal)	N	27	27	27	22	22
	Mean	7.66	2462.22	11615.41	12848.92	1.51
	SD	1.64	1205.51	9198.38	11774.74	-
	CV%	21	49	79	92	79
C (90 mg TAK-390MR 30 minutes before a meal)	N	27	27	27	24	24
	Mean	5.40	2770.56	12378.36	13516.12	1.68
	SD	4.90	1414.22	12672.69	15365.37	-
	CV%	91	51	102	114	63
D (90 mg TAK-390MR 1 hour before a meal)	N	27	27	27	23	23
	Mean	3.96	2549.26	12038.44	13473.25	1.94
	SD	2.48	1233.22	10327.86	12330.22	-
	CV%	63	48	86	92	56

a Harmonic Mean

Bioavailability of TAK-390 administered under fed conditions relative to the fasted state.

Parameter	Point Estimate	90% Confidence Interval
Regimen B (Test) versus Regimen A (Reference)		
C_{max}	1.3772	(1.1752 - 1.6138)
AUC_t	1.3723	(1.2443 - 1.5135)
AUC_{∞}	1.3744	(1.2527 - 1.5079)
Regimen C (Test) versus Regimen A (Reference)		
C_{max}	1.5520	(1.3244 - 1.8186)
AUC_t	1.3376	(1.2128 - 1.4752)
AUC_{∞}	1.3469	(1.2319 - 1.4727)
Regimen D (Test) versus Regimen A (Reference)		
C_{max}	1.3628	(1.1652 - 1.5939)
AUC_t	1.2773	(1.1595 - 1.4070)
AUC_{∞}	1.3457	(1.2308 - 1.4713)

Relative bioavailability of TAK-390 administered under various fed conditions.

Parameter	Point Estimate	90% Confidence Interval
Regimen B versus Regimen C		
C_{max}	0.8874	(0.7557 - 1.0421)
AUC_t	1.0260	(0.9291 - 1.1330)
AUC_{∞}	1.0204	(0.9263 - 1.1240)
Regimen C versus Regimen D		
C_{max}	1.1388	(0.9716 - 1.3347)
AUC_t	1.0472	(0.9494 - 1.1550)
AUC_{∞}	1.0009	(0.9111 - 1.0997)

Safety:

All 28 volunteers received at least one dose of TAK-390 and were included in the safety analysis. Three volunteers were withdrawn for abnormal laboratory values; 2 had elevations in serum creatinine and 1 had elevated serum ALT and GGT.

All Treatment-Emergent Adverse Events by Dosing Regimen.

MedDRA High Level Term/ Preferred Term(s)	Regimen A N=27	Regimen B N=27	Regimen C N=27	Regimen D N=27	All Regimens N=28
Total subjects with at least 1 adverse event	2 (7%)	4 (15%)	4 (15%)	2 (7%)	10 (36%)
Headaches NEC/ Headache	0	1 (4%)	2 (7%)	1 (4%)	3 (11%)
Administration Site Reaction NEC/ Venipuncture Site Pain, Venipuncture Site Reaction	0	0	1 (4%)	1 (4%)	2 (7%)
Renal Function Analyses/ Blood Creatinine Increased	0	1 (4%)	1 (4%)	0	2 (7%)
Faeces Abnormal/ Loose Stools	0	1 (4%)	0	0	1 (4%)
Flatulence, Bloating and Distension/ Flatulence	0	1 (4%)	0	0	1 (4%)
Gastrointestinal Atonic and Hypomotility Disorders NEC/ Gastroesophageal Reflux Disease	0	1 (4%)	0	0	1 (4%)
Liver Function Analyses/ Alanine Aminotransferase Increased, Gamma-Glutamyltransferase Increased	0	0	0	1 (4%)	1 (4%)
Neurological Signs and Symptoms NEC/ Dizziness	1 (4%)	0	0	0	1 (4%)
Purpura and Related Conditions/ Ecchymosis	0	0	0	1 (4%)	1 (4%)
Upper Respiratory Tract Signs and Symptoms/ Throat Irritation	1 (4%)	0	0	0	1 (4%)

Note: Regimen A (dosed while fasting), Regimen B (dosed 30 minutes after the start of a meal), Regimen C (dosed 30 minutes before a meal), and Regimen D (dosed 1 hour before a meal)
 NEC = not elsewhere classified

COMMENTS

1. The effect of food on the early phase of absorption is consistent with previous studies of lansoprazole delayed-release (DR) capsules. Type 1 granules, containing 25% of the total dose, use the same coat as the currently-marketed lansoprazole DR granules and are designed to release drug upon entry into the duodenum. Studies with lansoprazole DR capsules showed that C_{max} and AUC decreased by about half if administered 30 minutes *after* a meal but administering the dose at least 30 minutes *before* food intake had no effect on PK parameters.
2. Food intake increases C_{max} by 36-55% and AUC by 28-37% compared to Regimen A in which volunteers fasted for 4 hours post-dose. The 90% confidence intervals for C_{max} , AUC_t , and AUC_{inf} comparing Regimens A,B, or C (fed) to regimen A (fasting) all exclude 1 and are therefore statistically significantly different. The increase in these parameters likely represents the effect of Type 2 granules, containing 75% of the total dose, which are designed to release drug in the distal small intestine.
3. The 90% confidence intervals for C_{max} , AUC_t , and AUC_{inf} among the three feeding conditions are not statistically significantly different. Mean concentration versus time profiles nearly overlap for Regimens C and D in which TAK-390 was administered up to an hour *prior* to food intake. The mean concentration versus time profile for Regimen B (dose *after* food) does not overlap with Regimens C and D but is skewed to the right. Overall values for C_{max} , AUC_t , and AUC_{inf} for Regimen B compared to Regimens C and D are similar.
4. T_{max} increased by a mean of 2 - 4 hours when food was administered *prior* to dosing. Food intake *following* drug administration had no effect on T_{max} . The

pharmacodynamic consequences of the delay in T_{max} are addressed in the following study.

5. TAK-390 is generally well-tolerated by healthy volunteers. Headache was the most common adverse event (n=3, 11%) followed by venipuncture site pain (n=2, 7%) and elevated serum creatinine (n=2, 7%). Less frequent adverse events include loose stools, flatulence, GERD, elevated liver function tests, dizziness, ecchymosis, and throat irritation.

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Food Effect on Pharmacodynamics Study T-P106-146

Study Title: A Phase 1, Open-Label, Single-Dose, Four-Way Crossover Study to Assess the Effect of the Timing of Food on the Pharmacokinetics and Intragastric pH of Dexlansoprazole Following a Single Oral Dose of 90-mg Dexlansoprazole MR

Study Site:
(b) (4)

Objectives:

To evaluate the effect of the timing of food on the pharmacodynamics and pharmacokinetics of dexlansoprazole following a single oral dose of 90mg of dexlansoprazole MR.

Study Design:

This was a Phase 1, single-center, open-label, single-dose, randomized, 4-period crossover study in 48 healthy volunteers. Volunteers received a single dose of placebo on Day 1 and a single 90mg dose of dexlansoprazole on Day 3 of each of the four periods. The timing of food intake relative to dexlansoprazole dosing varied by regimen. Investigators randomly assigned the volunteer to one of four treatment sequence groups which determined the order of dosing regimens. A minimum washout of 5 days separated each period.

Treatment Sequence and Dosing Regimens

Sequence Group	Number of Subjects	Dosing Regimens			
		Period 1	Period 2	Period 3	Period 4
1	12	Regimen A	Regimen B	Regimen C	Regimen D
2	12	Regimen B	Regimen D	Regimen A	Regimen C
3	12	Regimen C	Regimen A	Regimen D	Regimen B
4	12	Regimen D	Regimen C	Regimen B	Regimen A

Regimen A: On Day 1, a single, oral dose of placebo was administered following a 10-hour fast. Subjects continued to fast until 4 hours postdose. On Day 3, a single, oral dose of 90 mg of dexlansoprazole MR was administered following a 10-hour fast. Subjects continued to fast until 4 hours postdose. Breakfast was not served on Day 1 and Day 3. NOTE: Hereinafter in this report, Regimen A will be defined as "dosed under fasting conditions."

Regimen B: On Day 1, a standardized, high-fat breakfast was provided 30 minutes prior to a single, oral dose of placebo. On Day 3, a standardized, high-fat breakfast was provided 30 minutes prior to a single, oral dose of 90 mg of dexlansoprazole MR. On Days 1 and 3, the standardized breakfast was to be consumed within 25 minutes. NOTE: Hereinafter in this report, Regimen B will be defined as "dosed 30 minutes after the start of a high-fat breakfast."

Regimen C: On Day 1, a standardized, high-fat breakfast was provided 5 minutes after a single, oral dose of placebo. On Day 3, a standardized, high-fat breakfast was provided 5 minutes after a single, oral dose of 90 mg of dexlansoprazole MR. On Days 1 and 3, the standardized breakfast was to be consumed within 25 minutes. NOTE: Hereinafter in this report, Regimen C will be defined as "dosed 5 minutes before a high-fat breakfast."

Regimen D: On Day 1, a standardized, high-fat breakfast was provided 30 minutes after a single, oral dose of placebo. On Day 3, a standardized, high-fat breakfast was provided 30 minutes after a single, oral dose of 90 mg of dexlansoprazole MR. On Days 1 and 3, the standardized breakfast was to be consumed within 25 minutes. NOTE: Hereinafter in this report, Regimen D will be defined as "dosed 30 minutes before a high-fat breakfast."

Volunteers receiving Regimens B, C, & D were served the following standardized high-fat breakfast:

- 2 Eggs fried in butter
- 2 Strips of bacon

- 2 Slices of toast with butter
- 4 Ounces of hash brown potatoes
- 8 Ounces of whole milk

Key Inclusion Criteria

Healthy males and non-pregnant females ages 18-55 years of age with a BMI 18-30 kg/m² were eligible for the study.

Key Exclusion Criteria

Subjects with recent GI disease (within past 6 months), as well as a history of surgical intervention that may result in a change in drug absorption were excluded. The use of any renal or hepatic clearance-altering agents within the past 28 days was also cause for exclusion.

Study Population:

Forty-eight healthy adult males and females, aged 18-55, participated in the study.

Study Population Demographics

Demographic Variable	All Subjects (N = 48)
Gender (n [%])	
Male	29 (60.4)
Female	19 (39.6)
Ethnicity (n [%])	
Hispanic or Latino	5 (10.4)
Not Hispanic or Latino	43 (89.6)
Race (n [%])	
Black	11 (22.9)
White	37 (77.1)
Age (years)	
Mean ± SD	32.0 ± 10.70
Median	28.5
minimum - maximum	19 - 53
Weight (kilograms)	
Mean ± SD	76.1 ± 11.50
Median	74.9
minimum - maximum	57 - 108
Height (centimeters)	
Mean ± SD	171.8 ± 9.74
Median	172.4
minimum - maximum	152 - 194

Pharmacokinetics Measurement:

Blood samples for determination of dexlansoprazole concentration were drawn prior to dosing and post-dose at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 6.5, 7, 8, 10, 12, 14, 16, and 24 hours. The following parameters were calculated: C_{max}, t_{lag}, t_{max}, λ_z, t_{1/2}, AUC_t, AUC_{inf}, and CL/F.

Bioanalytical Analysis:

Plasma concentration of dexlansoprazole were determined using LC/MS/MS with lansoprazole-d₄ as the internal standards.

Analyte	Method	LLOQ	ULOQ	QC precision	QC accuracy
TAK-390	LC/MS/MS	5.00 ng/mL	1200 ng/mL	≤ 4.8%	-2.3 – 1.3%

Pharmacokinetics Results:

Summary of the Effect of Food and the Timing of Food on the PK Parameter Estimates Following a Single, Oral Dose of 90mg of Dexlansoprazole MR

Regimen	Measure	t _{lag} (h)	t _{max} (h)	C _{max} (ng/mL)	AUC _t (ng-h/mL)	AUC _∞ (ng-h/mL)	V _d /F (L)	CL/F (L/h)	t _{1/2} ^a (h)
A	N	46	46	46	46	37	37	37	37
	Mean	0.87	5.38	1485.63	6996.26	7057.65	39.59	16.65	1.82 (1.49)
	SD	0.61	1.94	808.09	3738.70	3749.13	28.33	8.54	1.09
	%CV	70	36	54	53	53	72	51	60
B	N	46	46	46	46	37	37	37	37
	Mean	1.91	7.63	1824.96	7998.50	8157.18	27.81	13.44	1.54 (1.25)
	SD	0.87	1.84	658.85	3855.53	3992.02	18.72	5.65	0.76
	%CV	45	24	36	48	49	67	42	50
C	N	46	46	46	46	37	37	37	37
	Mean	0.49	5.94	1653.00	7974.69	8198.13	24.09	13.26	1.40 (1.20)
	SD	0.66	2.45	717.73	3751.38	3909.87	9.97	5.59	0.68
	%CV	136	41	43	47	48	41	42	49
D	N	46	46	46	46	37	37	37	37
	Mean	0.53	4.73	1597.09	7447.75	7970.43	33.77	14.17	1.71 (1.39)
	SD	0.49	2.84	760.88	3843.37	4014.52	32.31	6.98	1.05
	%CV	92	60	48	52	50	96	49	61

Note: Regimen A = dosed under fasting conditions, Regimen B = dosed 30 minutes after the start of a high-fat breakfast, Regimen C = dosed 5 minutes before a high-fat breakfast, and Regimen D = dosed 30 minutes before a high-fat breakfast.

a Arithmetic mean (harmonic mean).

Bioavailability of Dexlansoprazole Administered Under Various Fed Conditions Relative to Administration Under Fasting Conditions

Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
Regimen B (Test) versus Regimen A (Reference)		
C _{max}	1.3065	1.1735 - 1.4547
AUC _t	1.1901	1.1249 - 1.2591
AUC _∞	1.2050	1.1449 - 1.2683
Regimen C (Test) versus Regimen A (Reference)		
C _{max}	1.1684	1.0494 - 1.3009
AUC _t	1.1910	1.1257 - 1.2600
AUC _∞	1.2096	1.1484 - 1.2740
Regimen D (Test) versus Regimen A (Reference)		
C _{max}	1.1165	1.0026 - 1.2432
AUC _t	1.0903	1.0305 - 1.1535
AUC _∞	1.1483	1.0887 - 1.2112

Note: Regimen A = dosed under fasting conditions, Regimen B = dosed 30 minutes after the start of a high-fat breakfast, Regimen C = dosed 5 minutes before a high-fat breakfast, and Regimen D = dosed 30 minutes before a high-fat breakfast.

Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm-transformed data.

Relative Bioavailability of Dexlansoprazole Administered Under Various Fed Conditions

Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
Regimen C (Test) versus Regimen B (Reference)		
C_{max}	0.8943	0.8031 - 0.9958
AUC_t	1.0007	0.9458 - 1.0588
AUC_{∞}	1.0038	0.9529 - 1.0574
Regimen D (Test) versus Regimen B (Reference)		
C_{max}	0.8545	0.7675 - 0.9514
AUC_t	0.9161	0.8659 - 0.9692
AUC_{∞}	0.9529	0.9037 - 1.0048
Regimen D (Test) versus Regimen C (Reference)		
C_{max}	0.9555	0.8582 - 1.0639
AUC_t	0.9154	0.8653 - 0.9685
AUC_{∞}	0.9494	0.8996 - 1.0019

Note: Regimen A = dosed under fasting conditions, Regimen B = dosed 30 minutes after the start of a high-fat breakfast, Regimen C = dosed 5 minutes before a high-fat breakfast, and Regimen D = dosed 30 minutes before a high-fat breakfast.

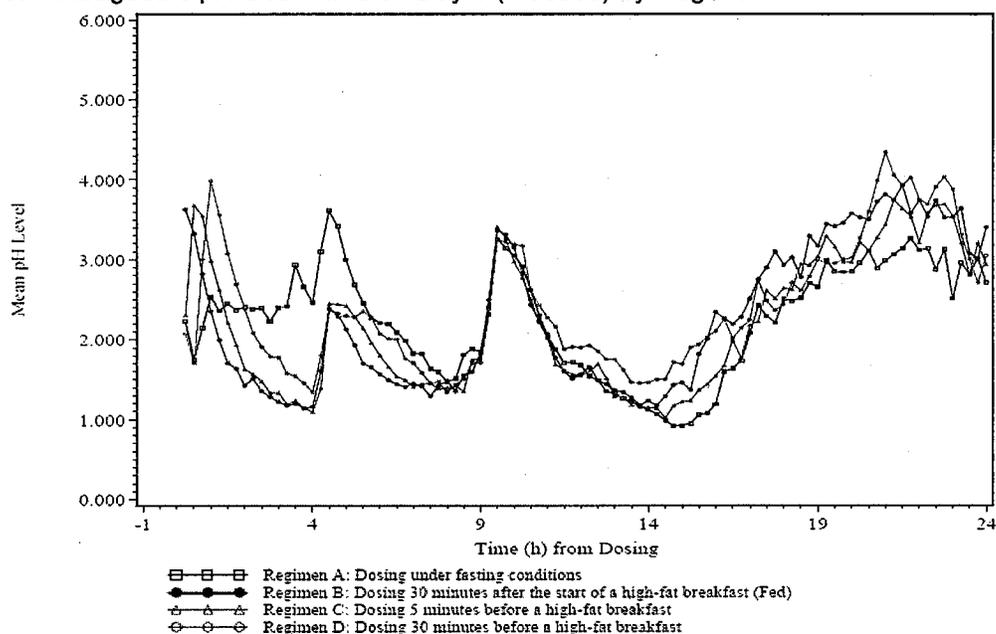
Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm-transformed data.

Pharmacodynamic Measurement:

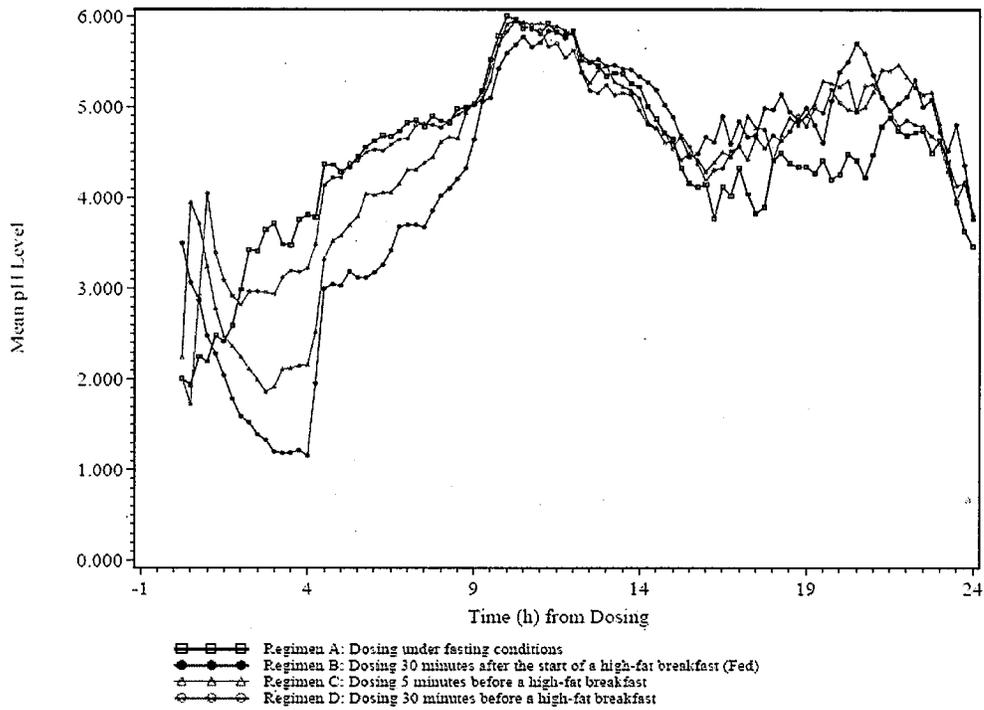
Intragastric pH was sampled every 4 seconds over the 24-hour dosing interval on Days 1 & 3. The median value over 15-minute intervals was calculated and used for the PD parameters. Other PD parameters that were calculated include the average pH over the entire 24-hour dosing interval and the following intervals: 0-4 hours, >4 to 9 hours, >9-12 hours, >12-16, and >16-24 hours. The percentage of time that intragastric pH was > 4 over the total 24-hour post-dose interval was determined. In addition, the percentage of time that pH was > 4 during the other intervals (0-4 hours, >4 to 9 hours, >9-12 hours, >12-16, and >16-24 hours) was calculated.

Pharmacodynamic Results:

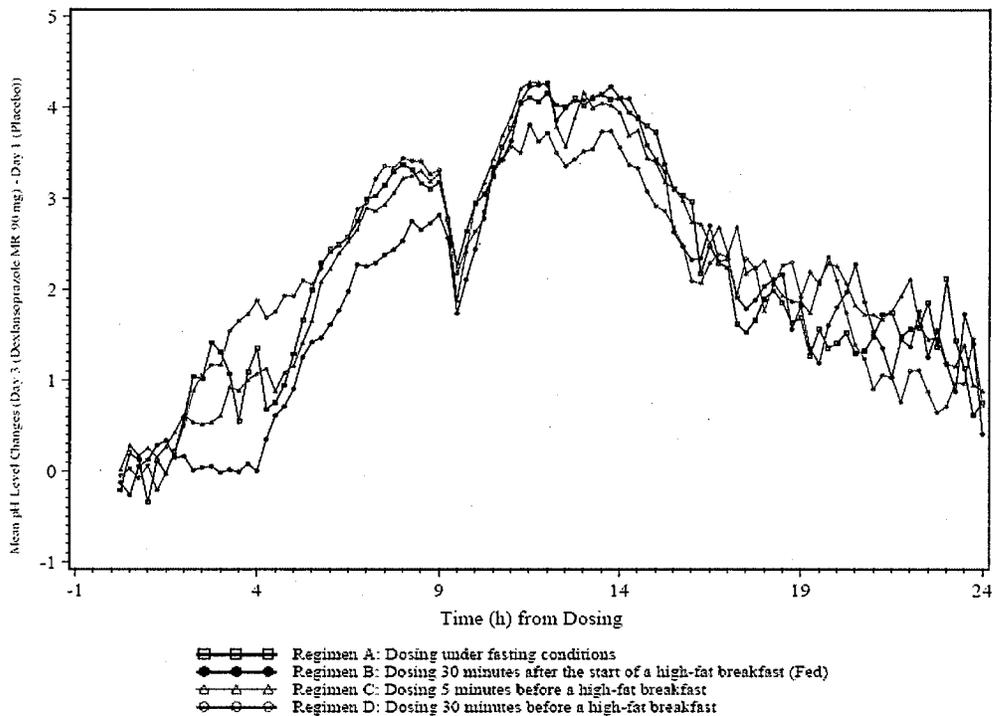
Mean Intragastric pH Over Time on Day 1 (Placebo) by Regimen



Mean Intragastric pH Over Time on Day 3 (Dexlansoprazole MR) by Regimen



Change From Baseline (Day 3 Minus Day 1) in Mean Intra-gastric pH Over Time, by Regimen



Percentage of Time Intra-gastric pH > 4 During 24-Hour Interval Post-Dose Following Placebo or Dexlansoprazole and the Change From Baseline

Analysis	Result for Each Dosing Regimen				p-value ^a for Pairwise Comparisons		
	A	B	C	D	Regimen B versus Regimen A ^b	Regimen C versus Regimen A ^b	Regimen D versus Regimen A ^b
Day 1 (Placebo)	17	18	16	19	0.897	0.548	0.547
Day 3 (Dexlansoprazole MR)	64	57	62	66	0.003***	0.222	0.544
Change from Baseline (Day 3 minus Day 1)	47	39	46	47	0.018*	0.642	0.993

Note: Regimen A = dosed under fasting conditions, Regimen B = dosed 30 minutes after the start of a high-fat breakfast, Regimen C = dosed 5 minutes before a high-fat breakfast, and Regimen D = dosed 30 minutes before a high-fat breakfast.

a The p-values are from an ANOVA with effects for regimen, sequence, period, and subject nested within sequence.

b Regimen A was defined as the reference regimen.

*, **, *** indicate $p \leq 0.05$, 0.01, or 0.001, respectively.

Safety:

Forty-six of the 48 volunteers completed all 4 dosing regimens. Two volunteers dropped out during the first washout period. Of the two withdrawals, one withdrew consent and the other experienced an elevation in hepatic enzymes.

Treatment-Emergent Adverse Events Experienced by ≥ 2 Volunteers Across All Regimens

MedDRA High Level Term MedDRA Preferred Term(s)	Total Across All Regimens N = 48
Total Subjects Experiencing at Least 1 Adverse Event	19 (40%)
Headaches NEC Headache	9 (19%)
Menstruation and Uterine Bleeding NEC Dysmenorrhoea	3 (6%)
Nausea and Vomiting Symptoms Nausea, Vomiting	3 (6%)
Upper Respiratory Tract Infections Nasopharyngitis, Upper Respiratory Tract Infection	3 (6%)

COMMENTS

1. C_{max} and AUCs of Regimens B (dose after food) and C (dose 5 minutes before food) increased by 17 – 31% compared to Regimen A (fasting). The 90% confidence intervals are outside the acceptable range for bioequivalence. The increases in this study are less than those noted in PK Study T-P104-069 in which C_{max} and AUC increased by up to 55% and 37%, respectively.
2. The C_{max} and AUCs of Regimen D (dose 30 minutes before food) were similar to Regimen A. The 90% confidence intervals are within the acceptable range for bioequivalence.
3. The percentage of *time intragastric pH* was > 4 over the 24 hour interval was less in Regimen B (food before dose) than in all other regimens. The decrease noted in Regimen B was statistically significant relative to Regimens A (fasting) and D (dose 30 minutes before food). The range was 57% - 66%, however, indicating only a 9% difference between the fed and fasted regimens.
4. Volunteers in Regimen B also had less *change in intragastric pH* over the 24-hour interval from baseline compared to all other regimens. Similar to time above pH 4, the change from baseline was statistically significant relative to

Regimens A (fasting) and D (dose 30 minutes before food). The differences in both time and change from baseline were driven largely by the period 4-9 hours post-dose. This correlates with the delayed absorption and decreased bioavailability of the Type 1 granules noted in PK Study T-P104-069.

5. Dexlansoprazole was well tolerated and no serious adverse events were noted. The most common adverse event was headache (n=9, 19%) followed by dysmenorrhea, nausea, vomiting, and upper respiratory tract infection (n=3, 6%).

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Food Effect Study CPH-001

Study Title: A Phase I, Randomized, Double-Blind, Placebo-Controlled, Ascending Single-Dose Study of the Safety, Tolerability, and Pharmacokinetics of TAK-390MR in Healthy Male Subjects

Study Site: (b) (4)

Objectives: The primary objective of this study was to determine the safety and PK of TAK-390MR in Japanese males. The secondary objective was to evaluate the effects of food on the safety and PK of single-dose TAK-390MR.

Study Design: This was a single-center, randomized, double-blind, single-dose, placebo-controlled study with 6 steps. Steps 1-5 were an ascending dose design (15mg – 120mg administered under fasted conditions) and included both extensive metabolizers (EMs) and poor metabolizers (PMs). In Step 6, EMs received a single 60mg dose of TAK-390MR or placebo in both fed and fasted states to evaluate the food effects on safety and PK.

Subject distribution and mode of administration for Step 6.

Step	Study Drug	Dose / Mode of Administration ¹⁾		# of Subjects ²⁾
		Period 1	Period 2	
6A	TAK-390MR 60 mg	Dosing one of TAK-390MR 60 mg capsule under fasting condition	Dosing one of TAK-390MR 60 mg capsule after breakfast	4 EMs
	TAK-390MR 60 mg placebo	Dosing one of TAK-390MR 60 mg placebo capsule under fasting condition	Dosing one of TAK-390MR 60 mg placebo capsule after breakfast	2 EMs
6B	TAK-390MR 60 mg	Dosing one of TAK-390MR 60 mg capsule after breakfast	Dosing one of TAK-390MR 60 mg capsule under fasting condition	4 EMs
	TAK-390MR 60 mg placebo	Dosing one of TAK-390MR 60 mg placebo capsule after breakfast	Dosing one of TAK-390MR 60 mg placebo capsule under fasting condition	2 EMs

1) The washout between period 1 and 2 was at least 1 week.

Plasma was collected for PK analysis for 48 hours post-dose.

Key Inclusion Criteria: Healthy Japanese males 20-35 years old, weighing at least 50kg, with a BMI of 18.5-24.9, and having specific CYP2C19 EM metabolizer genotypes were eligible to inclusion. The allowable genotypes were *1/*1, *1/*2, or *1/*3 for EMs.

Key Exclusion Criteria: Subjects with hepatic, renal, cardiovascular, hematological, or endocrine diseases were not eligible for this study.

Study Population:

Of the 113 subjects who were enrolled, 92 completed the study. The remaining 21 subjects did not receive the study drug because they were either replacements or were replaced by other subjects on the basis of exam results before study drug administration. The average age of the participants was 21.7 years. Subjects had an average height and weight of 170.8cm and 60.57kg, respectively. The genotypes and phenotypes were as follows:

Item / Category	Placebo	15mg	30mg	60mg	90mg	120mg	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)

CYP2C19 Genotype	1/1	3(15.0)	2(16.7)	2(16.7)	4(33.3)	3(25.0)	4(33.3)	18(22.5)
	1/2	6(30.0)	3(25.0)	1(8.3)	2(16.7)	2(16.7)	1(8.3)	15(18.8)
	1/3	1(5.0)	1(8.3)	3(25.0)	0(0.0)	1(8.3)	1(8.3)	7(8.8)
	2/2	6(30.0)	2(16.7)	2(16.7)	4(33.3)	2(16.7)	3(25.0)	19(23.8)
	2/3	3(15.0)	4(33.3)	3(25.0)	2(16.7)	3(25.0)	2(16.7)	17(21.3)
	3/3	1(5.0)	0(0.0)	1(8.3)	0(0.0)	1(8.3)	1(8.3)	4(5.0)
	homo EM	3(15.0)	2(16.7)	2(16.7)	4(33.3)	3(25.0)	4(33.3)	18(22.5)
hetero EM	7(35.0)	4(33.3)	4(33.3)	2(16.7)	3(25.0)	2(16.7)	22(27.5)	
TAK-390 Phenotype	PM	10(50.0)	6(50.0)	6(50.0)	6(50.0)	6(50.0)	6(50.0)	40(50.0)
	EM	10(50.0)	6(50.0)	6(50.0)	6(50.0)	6(50.0)	6(50.0)	40(50.0)
	PM	10(50.0)	6(50.0)	6(50.0)	6(50.0)	6(50.0)	6(50.0)	40(50.0)

Pharmacokinetic Measurement:

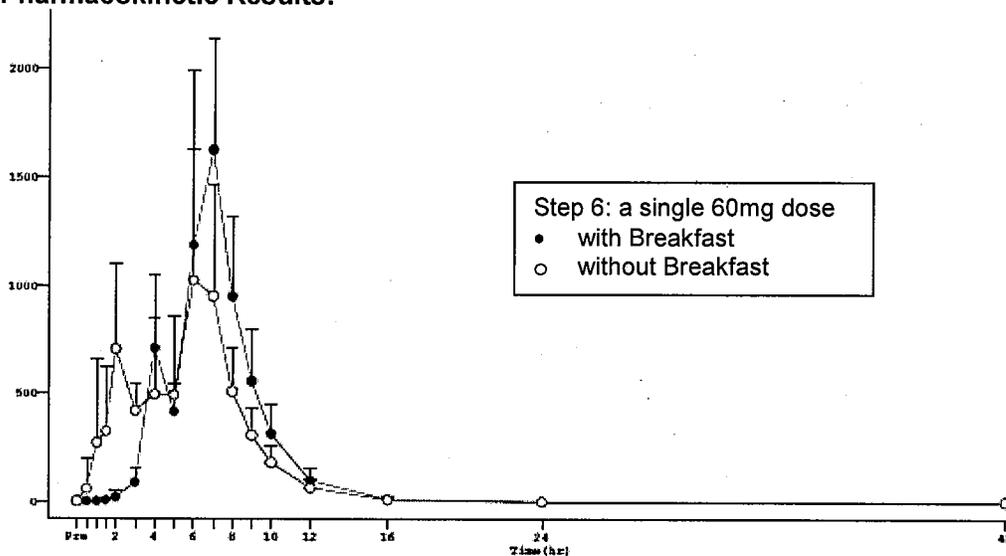
Both plasma and urine were collected for 48 hours post-dose in order to characterize the following parameters: t_{max} , C_{max} , AUC_{0-48} , AUC_{last} , AUC_{inf} , kel , $t_{1/2}$, & urinary excretion of the parent compound and metabolites.

Bioanalytical Analysis:

TAK-390 levels were measured by LC/MS/MS.

Analyte	Method	LLOQ	ULOQ	QC precision	QC accuracy
TAK-390	LC/MS/MS	5ng/mL	unknown	unknown	unknown

Pharmacokinetic Results:



PK parameters of a single 60mg dose of TAK-390MR in EMs under fed and fasted conditions.

Parameters	Dose Condition	Summary Statistics								
		N	Mean	SD	SE	Min	Q1	Median	Q3	Max
AUC ₀₋₄₈ (ng-hr/mL)	with Breakfast	8	6369.1	1515.88	535.95	3368	5659.0	6765.0	7154.0	8429
	without Breakfast	8	5557.1	1787.00	631.80	3075	4217.5	5480.5	6812.0	8362
AUClast (ng-hr/mL)	with Breakfast	8	6308.6	1492.42	527.65	3342	5621.0	6704.0	7070.0	8337
	without Breakfast	8	5521.9	1782.42	630.18	3049	4183.5	5458.5	6756.0	8330
MRTlast (hr)	with Breakfast	8	7.003	0.4042	0.1429	6.38	6.660	7.090	7.355	7.43
	without Breakfast	8	5.791	0.5667	0.2004	4.82	5.370	6.015	6.205	6.33
Cmax (ng/mL)	with Breakfast	8	1849.0	663.10	234.44	996	1317.0	1789.5	2312.5	2958
	without Breakfast	8	1292.6	561.64	198.57	728	920.5	1126.0	1545.0	2430
Cmax-1 (ng/mL)	with Breakfast	8	422.4	368.54	130.30	5	27.0	477.5	693.5	978
	without Breakfast	8	795.6	321.90	113.81	392	458.0	859.5	1102.0	1134
Cmax-2 (ng/mL)	with Breakfast	8	1681.0	667.27	235.91	996	1099.0	1614.0	2034.0	2958
	without Breakfast	8	1202.5	615.54	217.63	728	740.0	946.0	1545.0	2430
tmax (hr)	with Breakfast	8	6.63	0.518	0.183	6.0	6.00	7.00	7.00	7.0
	without Breakfast	8	4.88	2.031	0.718	2.0	3.00	5.50	6.50	7.0
tmax-1 (hr)	with Breakfast	8	3.188	1.1319	0.4002	1.50	2.000	4.000	4.000	4.00
	without Breakfast	8	1.813	1.0670	0.3772	0.50	1.000	2.000	2.000	4.00
tmax-2 (hr)	with Breakfast	8	6.000	1.3093	0.4629	4.00	5.000	6.500	7.000	7.00
	without Breakfast	8	5.625	1.7678	0.6250	2.00	5.000	6.000	7.000	7.00
AUCinf (ng-hr/mL)	with Breakfast	8	6341.0	1504.53	531.93	3357	5638.0	6741.5	7115.0	8382
	without Breakfast	8	5539.5	1783.34	630.51	3065	4200.5	5469.0	6784.5	8343
kel (hr ⁻¹)	with Breakfast	8	0.6054	0.12898	0.04560	0.432	0.5250	0.5890	0.6660	0.851
	without Breakfast	8	0.5505	0.10812	0.03823	0.459	0.4850	0.5280	0.5595	0.800
t _{1/2} (hr)	with Breakfast	8	1.1896	0.24176	0.08548	0.815	1.0445	1.1810	1.3230	1.605
	without Breakfast	8	1.2933	0.20024	0.07079	0.866	1.2415	1.3135	1.4295	1.511
CL/F (L/hr)	with Breakfast	8	10.14	3.355	1.186	7.2	8.45	8.90	10.65	17.9
	without Breakfast	8	11.90	4.056	1.434	7.2	8.95	10.95	14.30	19.6
MRTinf (hr)	with Breakfast	8	7.051	0.4119	0.1456	6.41	6.715	7.120	7.415	7.50
	without Breakfast	8	5.830	0.5761	0.2037	4.85	5.395	6.075	6.230	6.39

90% CI for the food effect on AUC₀₋₄₈.

Food Effect		Point Estimate	90% CI	
LS-Means			Lower	Upper
Fast	8.5762 (=ln(5303.500))	Fed-Fast 0.1525 (=ln(1.165))	0.0313 (=ln(1.032))	0.2738 (=ln(1.315))
Fed	8.7287 (=ln(6177.868))			

Fast:without Breakfast, Fed:with Breakfast

90% CI for the food effect on C_{max}.

Food Effect		Point Estimate	90% CI	
LS-Means			Lower	Upper
Fast	7.0903 (=ln(1200.296))	Fed-Fast 0.3729 (=ln(1.452))	0.1235 (=ln(1.131))	0.6224 (=ln(1.863))
Fed	7.4633 (=ln(1742.839))			

Fast:without Breakfast, Fed:with Breakfast

Safety:

Of the 68 volunteers who received a dose of study drug, there were only 2 reported adverse events. There was one report of an elevation in AST and a separate report of an elevation in ALT. Both of these AEs occurred in volunteers who received one 60mg dose of TAK-390MR under fasted conditions.

COMMENTS

1. AUC_{0-48} is increased by 16% (90% CI 3 to 31.5%) in fed subjects relative to those in the fasted state. This is slightly less than the increase observed in Caucasians (19 to 37%) under similar feeding conditions (dose after food).
2. C_{max} is increased by 45% (90% CI 13 to 86%) in fed subjects relative to those in the fasted state. The increase in C_{max} in Caucasians under similar conditions was 30 to 37%.

Bioequivalence Study T-P106-148

Study Title: A Phase 1, Open-Label, Two-Way Crossover Study to Assess the Bioequivalence of Dexlansoprazole MR 90mg When the Capsule Contents Are Administered Sprinkled Over Applesauce Relative to a Single, Oral Dose of Dexlansoprazole MR 90mg Intact Capsule Administered Orally

Study Sites:

(b) (4)

Objectives:

To evaluate the relative bioavailability and assess the bioequivalence of dexlansoprazole administered as granules or as an intact capsule.

Study Design:

This was an open-label, balanced, randomized, 2-treatment, 2-period, 2-sequence, crossover, single-dose, bioavailability/bioequivalence study comparing the exposures following administration of an intact dexlansoprazole capsule (90 mg) and dexlansoprazole granules (90 mg) in 60 healthy males and females. Volunteers were randomly assigned to the sequence in which they received each regimen. A minimum of 5 days separated each period. Blood sampling for PK analysis occurred up to 24 hours post-dose.

Formulations:

Reference formulation was the following product.

Intact dexlansoprazole capsule

The test formulation was the following product.

Dexlansoprazole granules

Sequence and Regimens to which Volunteers were Randomly Assigned

Sequence Group	Number of Subjects	Period 1	Period 2
1	30	Regimen A	Regimen B
2	30	Regimen B	Regimen A

Note: Regimen A = Granules from a single capsule of 90 mg of dexlansoprazole MR administered orally sprinkled over 1 tablespoon of applesauce. Regimen B = A single, intact capsule of 90 mg of dexlansoprazole MR administered orally.

Key Inclusion Criteria

Healthy males and non-pregnant females ages 18-55 years of age with a BMI 18-30 kg/m² were eligible for the study.

Key Exclusion Criteria

Subjects with current or recent GI disease (within past 6 months), as well as a history of surgical intervention that may result in a change in drug absorption were excluded. The use of any renal or hepatic clearance-altering agents within the past 28 days was cause for exclusion.

Study Population:

A total of 60 healthy adult males and females enrolled in the study. Of these volunteers, 51 (85.%) completed the study. Nine volunteers withdrew from the study due to either adverse events or withdrawal of consent.

The demographics are shown below.

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Demographic Variable	All Subjects (N = 60)
Gender (n [%])	
Male	48 (80.0)
Female	12 (20.0)
Ethnicity (n [%])	
Hispanic or Latino	13 (21.7)
Not Hispanic or Latino	47 (78.3)
Race (n [%])	
American Indian/Alaska Native	2 (3.3)
Asian	1 (1.7)
Black	36 (60.0)
White	20 (33.3)
Multiracial	1 (1.7)
Age (years)	
Mean ± SD	31.3 ± 8.27
Median	30.0
minimum - maximum	19 - 49
Weight (kilograms)	
Mean ± SD	75.5 ± 10.53
Median	76.7
minimum - maximum	51 - 100
Height (centimeters)	
Mean ± SD	174.0 ± 8.05
Median	172.7
minimum - maximum	157 - 193

Note: n = number of subjects in subset analyses.

Pharmacokinetic Measurement:

Blood samples were collected at the following time points during each period for the analysis of concentrations of Dexlansoprazole: prior to dosing, 30 minutes, and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours post-dose.

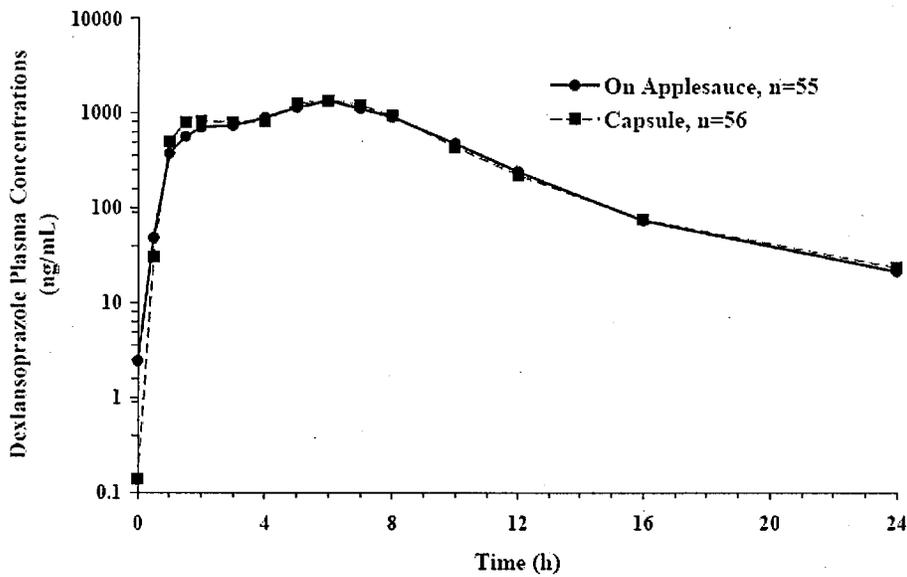
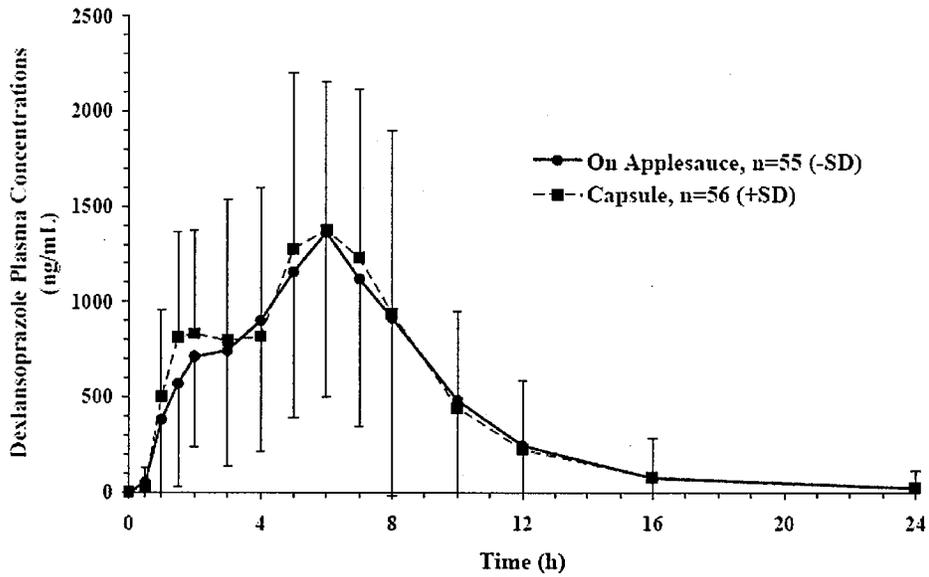
Bioanalytical Analysis:

Dexlansoprazole plasma concentrations were measured using LC/MS/MS.

Analyte	Method	LLOQ	ULOQ	QC precision	QC accuracy
Dexlansoprazole	LC/MS/MS	5 ng/mL	1200 ng/mL	< 3.9%	-0.8% - 4.2%

Pharmacokinetic Results:

Mean concentration-time profiles following administration of a single-dose of intact dexlansoprazole capsules and granules in healthy volunteers, are presented in the following figures.



A summary of dextansoprazole pharmacokinetic parameters following administration of a single-dose of intact dextansoprazole capsules and granules in healthy volunteers, is presented in the following table.

Regimen	Measure	t_{max} (h)	C_{max} (ng/mL)	AUC_t (ng·h/mL)	AUC_{∞} (ng·h/mL)	λ_z (h ⁻¹)	$t_{1/2}^a$ (h)	CL/F (L/h)	V_z/F (L)
A	N	50	50	50	49	49	49	49	49
	Mean	4.71	1840.76	10127.04	10416.48	0.43	2.08 (1.62)	12.92	32.16
	%CV	48	54	68	71	48	57	62	48
B	N	50	50	50	49	49	49	49	49
	Mean	4.73	1966.78	10736.08	11093.38	0.43	2.14 (1.63)	12.14	31.20
	%CV	44	56	72	75	47	60	62	58

Note: Regimen A = Granules from a single capsule of 90 mg of dexlansoprazole MR administered orally sprinkled over 1 tablespoon of applesauce. Regimen B = A single, intact capsule of 90 mg of dexlansoprazole MR administered orally.

a Arithmetic mean (harmonic mean).

A summary of statistical analysis of dexlansoprazole pharmacokinetic parameters following administration of dexlansoprazole capsules and granules in healthy volunteers, is presented in the following table.

Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
Regimen A versus Regimen B		
C_{max}	0.94	(0.8695 - 1.0225)
AUC_t	0.95	(0.8943 - 0.9998)
AUC_{∞}	0.94	(0.8898 - 0.9951)

Note: Regimen A = Granules from a single capsule of 90 mg of dexlansoprazole MR administered orally sprinkled over 1 tablespoon of applesauce. Regimen B = A single, intact capsule of 90 mg of dexlansoprazole MR administered orally.

Safety:

All 60 volunteers received at least one dose of dexlansoprazole and were included in the safety analysis. Nine volunteers withdrew from the study after the first treatment period. The reasons for discontinuation were as follows: positive drug screen (2), withdrawal of consent (2), adverse events (2), and lost to follow-up (3 - includes 2 who did not show for Period 2 but had final procedures performed). One volunteer experienced vomiting, ketonuria, and hypokalemia. Another volunteer experienced an elevation in white blood cell count.

COMMENTS

- Deslansoprazole administered as granules sprinkled over applesauce is bioequivalent to the same dose taken as an intact capsule. The 90% confidence intervals for C_{max} (86%-102%), AUC_t (89%-99%), and AUC_{inf} (88%-99%) were well within the range for bioequivalence.
- Other PK parameters including t_{max} , CL/F, and V/F are similar between both groups.
- Dexlansoprazole was well tolerated and no serious adverse events were noted. Nine volunteers experienced at least one adverse event, of which the most common was vomiting (n=3, 5%). All other events were reported in only one volunteer each and were not serious.

Phenytoin Drug Interaction Study T-P105-133

Study Title: A Phase 1, Double-Blind, Placebo-Controlled, Two-way Crossover Study to Assess the Effect of Multiple Oral Sodes of 90mg Dexlansoprazole MR on the Pharmacokinetics of Phenytoin Following a Single Oral Dose of 250mg Phenytoin.

Study Sites:

(b) (4)

Objectives:

To evaluate the effect of multiple once-daily doses of dexlansoprazole MR 90mg on the pharmacokinetics of a single 250mg dose of phenytoin.

Study Design:

This was a Phase 1, single-center, double-blind, placebo-controlled, randomized, two-way crossover study of dexlansoprazole MR or placebo with open-label phenytoin in 16 healthy volunteers. Each of the two periods was 9 days in length during which volunteers took dexlansoprazole or placebo once-daily on Days 1-9 and a single dose of phenytoin on Day 6 only. Phenytoin PK were studied for 96 hours post-dose. A minimum 7-day washout interval passed between the last dose in Period 1 and the first dose in Period 2.

Sequence	Number of Subjects	Regimens	
		Period 1	Period 2
1	8	Regimen A	Regimen B
2	8	Regimen B	Regimen A

Regimen A: 90 mg dexlansoprazole MR once-daily for 9 consecutive days plus a single oral dose of 250 mg phenytoin (10 mL of 125 mg/5 mL Dilantin-125 oral suspension administered via oral syringe) on Day 6.

Regimen B: Placebo for dexlansoprazole MR once-daily for 9 consecutive days plus a single oral dose of 250 mg phenytoin (10 mL of 125 mg/5 mL Dilantin-125 oral suspension administered via oral syringe) on Day 6.

Sample Size Determination

Investigators determined that a sample size of 16 volunteers (8 per sequence) provided a $\geq 95\%$ probability of concluding no effect of dexlansoprazole on phenytoin AUC if the true difference was no more than 5%. Investigators assumed an intrasubject variance of 0.012 for the natural logarithm of AUC.

Key Inclusion Criteria

Healthy males and non-pregnant females ages 18-55 years of age with a BMI 18-30 kg/m² were eligible for the study.

Key Exclusion Criteria

Subjects with current or recent GI disease (within past 6 months), as well as a history of surgical intervention that may result in a change in drug absorption. Use of any renal or hepatic clearance-altering agents within the past 28 days.

Study Population:

Baseline demographic characteristics

Variable	All Subjects N=16
Gender n (%)	
Male	14 (87.5)
Female	2 (12.5)
Ethnicity n (%)	
Hispanic or Latino	2 (12.5)
Not Hispanic or Latino	14 (87.5)
Race n (%)	
Black	6 (37.5)
White	10 (62.5)
Age (yr)	
Mean	25.8
SD	4.61
Median	25.0
Min-Max	20-35
Weight (kg)	
Mean	80.4
SD	10.73
Median	79.4
Min-Max	63-105
Height (cm)	
Mean	178.3
SD	7.74
Median	178.8
Min-Max	165-193

Genotype Analysis:

No volunteers were homozygous for the mutant allele of either 2C9 or 2C19.

Subject	2C9 Genotype	2C19 Genotype
101	wt / wt	*2 / wt
102	wt / wt	*2 / wt
103	wt / wt	wt / wt
104	*2 / wt	wt / wt
105	wt / wt	wt / wt
106	wt / wt	wt / wt
107	wt / wt	wt / wt
108	*2 / wt	wt / wt
109	wt / wt	wt / wt
110	wt / wt	*2 / wt
111	did not consent	did not consent
112	wt / wt	wt / wt
113	*2 / wt	wt / wt
114	wt / wt	wt / wt
115	*2 / wt	wt / wt
116	wt / wt	wt / wt

Pharmacokinetic Measurement:

Beginning on Day 6, blood samples for the determination of phenytoin concentration were drawn prior to dosing and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, and 96 hours post-dose. The following parameters were calculated: C_{max} , t_{lag} .

t_{max} , λ_z , $t_{1/2}$, AUC_t , AUC_{inf} , and CL/F . Blood samples for determination of dexlansoprazole concentration were drawn prior to dosing and at 4 and 24 hours post-dose.

Bioanalytical Analysis:

Analyte	Method	LLOQ	ULOQ	QC precision	QC accuracy
Dexlansoprazole	LC/MS/MS	5 ng/mL	1200 ng/mL	≤3.1%	-2.3% to 3.0%
Phenytoin	LC/MS/MS	10 ng/mL	4000 ng/mL	≤6.9%	-2.0% to 2.0%

Pharmacokinetic Results:

Phenytoin Concentration

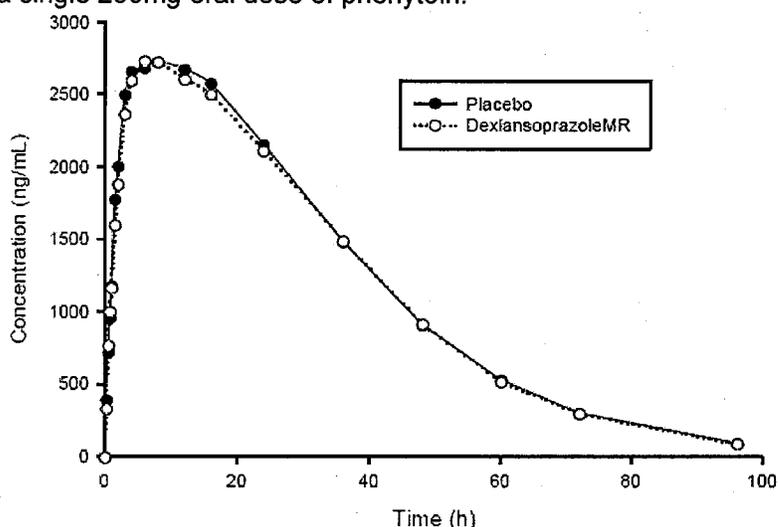
Summary of PK parameters for phenytoin following a single 250mg oral dose of phenytoin during each Regimen.

	t_{max} (h)	C_{max} ($\mu\text{g/mL}$)	AUC_t ($\mu\text{g}\cdot\text{h/mL}$)	AUC_{∞} ($\mu\text{g}\cdot\text{h/mL}$)	V_z/F (L)	CL/F (L/h)	$t_{1/2}^a$ (h)
90 mg Dexlansoprazole MR & 250 mg Phenytoin (Regimen A)							
N	16	16	16	16	16	16	16
Mean	7.56	2.85	111.90	113.99	44.60	2.35	13.55 (13.14)
SD	5.33	0.61	27.04	28.53	10.51	0.73	2.46
CV (%)	70	21	24	25	24	31	18
Placebo & 250 mg Phenytoin (Regimen B)							
N	16	16	16	16	16	16	16
Mean	9.16	2.92	113.41	115.62	43.75	2.29	13.65 (13.12)
SD	5.42	0.60	26.18	27.71	9.25	0.58	2.92
CV (%)	59	20	23	24	21	25	21

Regimen A: 90 mg dexlansoprazole MR once-daily for 9 consecutive days plus a single 250 mg dose of phenytoin.

Regimen B: Placebo once-daily for 9 consecutive days plus a single 250 mg dose of phenytoin.

Mean plasma concentrations of phenytoin versus time profiles following administration of a single 250mg oral dose of phenytoin.



Bioavailability of phenytoin with dexlansoprazole relative to phenytoin with placebo.

Parameter	Point Estimate	90% Confidence Interval
C _{max}	0.9726	(0.8937 - 1.0584)
AUC _t	0.9820	(0.9380 - 1.0282)
AUC _∞	0.9811	(0.9363 - 1.0281)

Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm transformed data.

Dexlansoprazole Concentration

Subject Sequence pre-dose 4 h 24 h

Regimen A: Dexlansoprazole MR 90 mg QD (Days 1-9) with a single oral dose of 250 mg phenytoin (Day 6)

101	BA	<5.0*	1790.0	9.4
102	AB	22.4	2810.0	32.0
103	BA	<5.0*	1710.0	<5.0*
104	AB	<5.0*	3260.0	<5.0*
105	BA	16.0	698.0	18.0
106	AB	<5.0*	1800.0	5.3
107	AB	<5.0*	355.0	<5.0*
108	BA	<5.0*	3010.0	<5.0*
109	AB	<5.0*	1030.0	<5.0*
110	BA	<5.0*	1120.0	<5.0*
111	BA	<5.0*	1040.0	<5.0*
112	AB	12.0	529.0	15.0
113	AB	<5.0*	1680.0	<5.0*
114	BA	<5.0*	492.0	<5.0*
115	BA	14.3	1960.0	8.6
116	AB	<5.0*	1590.0	<5.0*

Safety:

All 16 volunteers received at least one dose of study drug; therefore, all volunteers were included in the safety analysis. No volunteers withdrew from the study prematurely due to adverse events. There were no serious or significant adverse events reported during the study.

MedDRA High-Level Term MedDRA Preferred Term(s)	Treatment Regimen	
	Regimen A (N=16) n (%)	Regimen B (N=16) n (%)
Subjects Reporting at Least One Adverse Event	5 (31)	4 (25)
Injection And Infusion Site Reactions	2 (13)	2 (13)
Infusion Site Bruising		
Infusion Site Pain		
Infusion Site Thrombosis		
Non-Site Specific Injuries NEC	0 (0)	2 (13)
Excoriation		
Application And Instillation Site Reactions	0 (0)	1 (6)
Application Site Dermatitis		
Breathing Abnormalities	1 (6)	0 (0)
Dyspnoea		
Dermatitis and Eczema	1 (6)	0 (0)
Dermatitis Contact		
Flatulence, Bloating, and Distension	1 (6)	0 (0)
Flatulence		
Nasal Congestion And Inflammations	0 (0)	1 (6)
Nasal Congestion		
Nasal Disorders	1 (6)	0 (0)
Epistaxis		
Radiation Injuries	0 (0)	1 (6)
Sunburn		

Regimen A: Dexlansoprazole MR 90 mg once-daily (Days 1-9) with a single oral dose of 250 mg phenytoin (Day 6).

Regimen B: Placebo once-daily (Days 1-9) with a single oral dose of 250 mg phenytoin (Day 6).

COMMENTS:

1. Phenytoin PK parameters do not change when administered as a single 250mg dose with either 90mg dexlansoprazole or placebo given once daily. The 90% confidence intervals for C_{max} and AUC are within the 80-125% range for bioequivalence.
2. There is no differences in dexlansoprazole C_{min} for those volunteers who express the wild-type 2C19 relative to *2 heterozygotes. Unlike the warfarin study, there were no *2 homozygotes; therefore, the impact of this mutation on dexlansoprazole and phenytoin PK cannot be assessed.

Warfarin Drug Interaction Study T-P105-132

Study Title: A Phase 1 Two-Way Crossover Study to Assess the Effect of Multiple Oral Doses of Dexlansoprazole MR (TAK-390MR) on the Single Oral Dose Pharmacokinetics and Pharmacodynamics of Warfarin

Study Sites:

(b) (4)

Objectives:

To evaluate the effect of multiple once-daily doses of dexlansoprazole MR 90mg on the pharmacokinetics and pharmacodynamics of a single warfarin 25mg dose.

Study Design:

This was a Phase 1, single-center, double-blind, placebo-controlled, randomized, two-way crossover study of dexlansoprazole MR or placebo with open-label warfarin in 19 healthy male volunteers. Each of the two periods was 11 days in length during which volunteers took dexlansoprazole or placebo once-daily on Days 1-11 and a single dose of warfarin on Day 6 only. Warfarin PK and PD were studied for 144 hours post-dose. A minimum 10-day washout interval passed between the last dose in Period 1 and the first dose in Period 2.

Sequence and regimens to which volunteers were randomly assigned.

Sequence	Number of Subjects	Regimens	
		Period 1	Period 2
1	10	Regimen A	Regimen B
2	10	Regimen B	Regimen A

Regimen A: Dexlansoprazole MR 90 mg once-daily for 11 consecutive days & a single oral 25 mg warfarin dose on Day 6.

Regimen B: Placebo once-daily for 11 consecutive days & a single oral 25 mg warfarin dose on Day 6.

Sample Size Determination

Investigators determined that a sample size of 20 volunteers (10 per sequence) provided a $\geq 90\%$ probability of concluding no effect of dexlansoprazole on S-warfarin C_{max} , S-warfarin AUC, R-warfarin C_{max} , and R-warfarin AUC if the true difference was no more than 5%. Investigators assumed an intrasubject variance of 0.023.

Key Inclusion Criteria

Healthy males and non-pregnant females ages 18-55 years of age with a BMI 18-30 kg/m^2 were eligible for the study.

Key Exclusion Criteria

Subjects with current or recent GI disease (within past 6 months), as well as a history of surgical intervention that may result in a change in drug absorption. Use of any renal or hepatic clearance-altering agents within the past 28 days. A history of coagulopathy, bleeding disorder or blood dyscrasia. Baseline INR > 1.2 at the start of Period 1.

Study Population:

Variable	All Subjects N=19
Gender n (%)	
Male	19 (100)
Female	0
Ethnicity n (%)	
Hispanic or Latino	1 (5.3)
Not Hispanic or Latino	18 (94.7)
Race n (%)	
American Indian/Alaska Native	1 (5.3)
Black	5 (26.3)
White	9 (47.4)
Multiracial	4 (21.1)
Age (yr)	
Mean	33.7
SD	9.31
Median	33.0
Min-Max	18-48
Weight (kg)	
Mean	83.3
SD	10.11
Median	82.6
Min-Max	60-108
Height (cm)	
Mean	179.4
SD	7.48
Median	177.8
Min-Max	163-193

max = maximum; min = minimum.

Pharmacokinetic Measurement:

Beginning on Day 6, blood samples for determination of warfarin concentration were drawn prior to dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120, and 144 hours post-dose. The following parameters were calculated: C_{max} , t_{lag} , t_{max} , λ_z , $t_{1/2}$,

AUC_t, AUC_{inf}, and CL/F. Blood samples for determination of dextlansoprazole concentration were drawn prior to dosing and at 4 and 24 hours post-dose.

Bioanalytical Analysis:

Analyte	Method	LLOQ	ULOQ	QC precision	QC accuracy
Dextlansoprazole	LC/MS/MS	5 ng/mL	1200 ng/mL	< 3.2%	-2.8% to 3.3%
R- and S-Warfarin	LC/MS/MS	5 ng/mL	1500 mg/mL	≤15%	-4.3% to 3.6%

Pharmacokinetics Results:

Summary of PK parameter estimates for R- and S-warfarin following a single 25mg oral dose.

Regimen		t _{max} (h)	C _{max} (µg/mL)	AUC _t (µg·h/mL)	AUC _∞ (µg·h/mL)	t _{1/2} ^a (h)	CL/F (mL/h)	V _f /F (L)
R-Warfarin								
Regimen A	N	18	18	18	18	18	18	18
	Mean	1.03	1.63	73.03	85.07	49.04 (46.75)	304.69	20.96
	CV (%)	170	15	14	19	22	21	17
Regimen B	N	18	18	18	18	18	18	18
	Mean	1.76	1.52	71.05	82.15	48.81 (46.29)	314.29	21.63
	CV (%)	203	13	14	18	22	19	20
S-Warfarin								
Regimen A	N	18	18	18	18	18	18	18
	Mean	0.67	1.72	50.11	54.54	42.06 (40.48)	488.49	29.02
	CV (%)	37	17	23	26	21	26	25
Regimen B	N	18	18	18	18	18	18	18
	Mean	0.95	1.58	47.92	51.76	40.12 (38.90)	510.37	29.12
	CV (%)	47	16	21	24	18	25	26

Regimen A: 90 mg dextlansoprazole MR once-daily for 11 consecutive days plus a single oral 25 mg warfarin dose on Day 6.

Regimen B: Placebo once-daily for 11 consecutive days plus a single oral 25 mg warfarin dose on Day 6.

CV (%) = percent coefficient of variation.

^a Arithmetic mean (harmonic mean).

Bioavailability of warfarin with dextlansoprazole relative to that of warfarin with placebo.

Parameter	Point Estimate	90% Confidence Interval
R-Warfarin		
C _{max}	0.93	(0.8601 - 1.0027)
AUC _t	0.97	(0.9544 - 0.9936)
AUC _∞	0.97	(0.9433 - 0.9923)
S-Warfarin		
C _{max}	0.93	(0.8397 - 1.0199)
AUC _t	0.96	(0.9325 - 0.9917)
AUC _∞	0.95	(0.9232 - 0.9860)

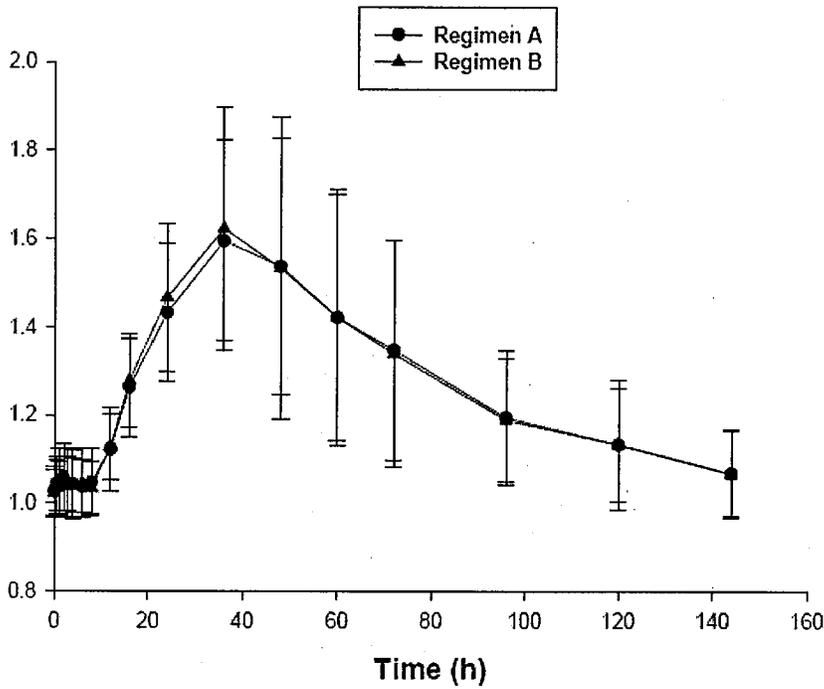
Note: The point estimates and confidence intervals were obtained from the exponentiated results of analysis of the natural logarithm transformed data.

Pharmacodynamic Measurement:

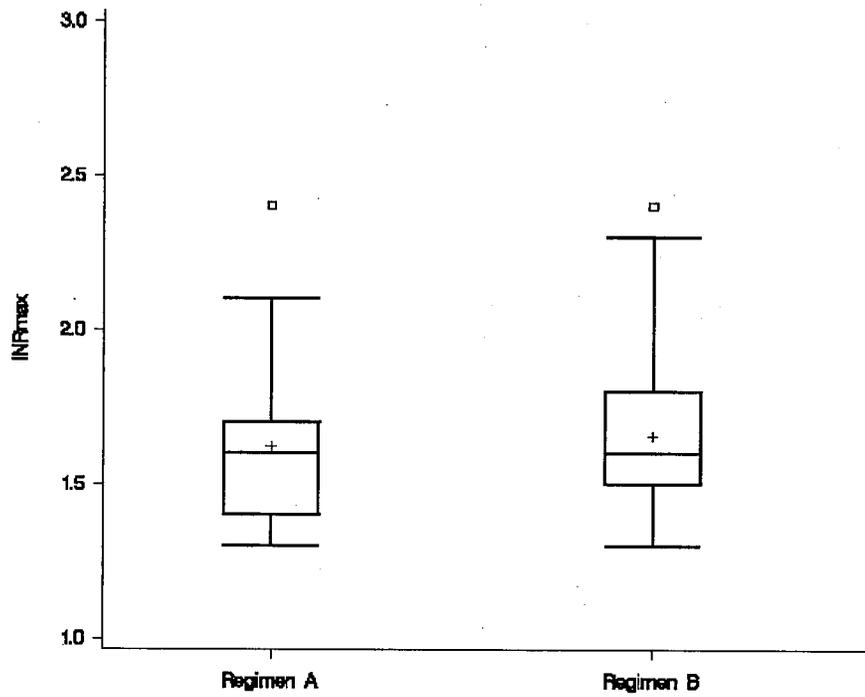
Beginning on Day 6, blood samples for determination of INR were drawn prior to dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60, 72, 96, 120, and 144 hours post-dose. The effect of dexlansoprazole on warfarin PD was assessed through ANOVA on the PD parameters INR_{144} and INR_{max} . The INR_{144} is the area under the INR-time curve from time 0 to 144 hours following warfarin administration.

Pharmacodynamic Results:

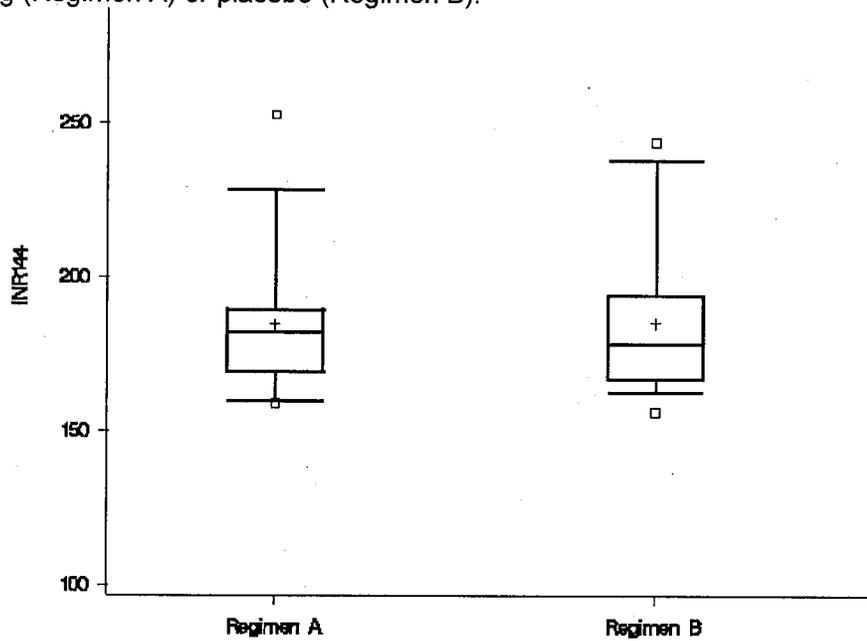
INR-Time profiles following administration of 25mg warfarin with either dexlansoprazole 90mg (Regimen A) or placebo (Regimen B).



Box plot of INR_{max} following a single 25mg oral dose of warfarin with dexlansoprazole 90mg (Regimen A) or placebo (Regimen B).



Box plot of INR₁₄₄ following a single 25mg oral dose of warfarin with dexlansoprazole 90mg (Regimen A) or placebo (Regimen B).



Statistical analysis of warfarin PD parameters.

Regimen		INR ₁₄₄ (N=18)	INR _{max} (N=18)
Dexlansoprazole MR & Warfarin (Regimen A)	Mean	184.404	1.622
	SD	23.949	0.284
Placebo & Warfarin (Regimen B)	Mean	184.798	1.656
	SD	23.927	0.311
Difference in Least Square Means (Regimen A - Regimen B)		0.184	-0.019
p-value		0.910	0.362

Safety:

All 19 volunteers received at least one dose of dexlansoprazole and warfarin and are included in the safety analysis. One volunteer withdrew from the study following a positive drug screen. No volunteers prematurely discontinued due to an adverse event or elevated INR.

MedDRA High-Level Term MedDRA Preferred Term(s)	Treatment Regimen	
	Regimen A (N=19) n (%)	Regimen B (N=18) n (%)
Subjects Reporting at Least One Adverse Event	2 (11)	3 (17)
Headaches NEC Headaches	1 (5)	1 (6)
Musculoskeletal And Connective Tissue Signs And Symptoms NEC Back Pain Pain in Extremity	1 (5)	1 (6)
Dermal And Epidermal Conditions NEC Skin Lesion	0 (0)	1 (6)
Gastrointestinal Atonic And Hypomotility Disorders NEC Constipation	0 (0)	1 (6)
Pain and Discomfort Chest Pain	0 (0)	1 (6)
Rashes, Eruptions And Exanthems NEC Rash	0 (0)	1 (6)
Upper Respiratory Tract Signs And Symptoms Dry Throat	0 (0)	1 (6)

Regimen A: 90 mg dexlansoprazole MR once-daily for 11 consecutive days plus a single oral 25 mg warfarin dose on Day 6.

Regimen B: Placebo once-daily for 11 consecutive days plus a single oral 25 mg warfarin dose on Day 6.

COMMENTS

1. Warfarin PK parameters do not change when administered as a single 25mg dose with either 90mg dexlansoprazole or placebo given once daily. The 90% confidence intervals for C_{max}, AUC_t, and AUC_{inf} of both R- and S-warfarin were within the 80-125% range for bioequivalence.
2. Both INR_{max} and INR₁₄₄ (area under the INR-time curve up to hour 144) were similar between Regimens A and B.
3. One volunteer (#101), the only homozygote for the CYP 2C19*2 allele, had greatly elevated dexlansoprazole troughs relative to heterozygotes and those who were homozygous for the wild-type allele. This same volunteer had a peak plasma concentration that was similar to others, a result that would be consistent

with reduced clearance secondary to the CYP2C19 polymorphism. The clinical significance of this observation is unknown.

Appears This Way On Original

From: Grosser, Stella C
Sent: Tuesday, July 01, 2008 12:20 PM
To: Bai, Jane
Subject: RE: NDA 22287
Hi Jane,

There appears to be no association statistically between genotype and cardiac effects. A chi-square test for association gave a p-value of 0.30. Fisher's exact test, which is more appropriate here given the small numbers experiencing effects in both groups, gave a p-value of 0.40. Both results are far from significant.

Stella

From: Bai, Jane
Sent: Thursday, June 19, 2008 8:12 AM
To: Grosser, Stella C
Subject: NDA 22287

Hi Stella:

In the wt/wt group, 3 out of 148 subjects experienced cardiac side effects and in the wt*2 group 0 out of 53 subjects experienced cardiac effects.

Please kindly comment by e-mail whether or not there is statistical significance.

Thanks,

Jane

Appears This Way On Original

From: Grosser, Stella C
Sent: Tuesday, July 01, 2008 12:31 PM
To: Bai, Jane
Cc: Lee, Sue Chih H
Subject: RE: NDA 22287
Hi Jane,

There appears to be no association statistically between genotype and AE's. A chi-square test for association gave a p-value of 0.12. Fisher's exact test, which is more appropriate here given the small numbers in the PM group, gave a p-value of 0.15. Both results are insignificant.

Stella

From: Bai, Jane
Sent: Monday, June 30, 2008 11:10 AM
To: Grosser, Stella C
Cc: Lee, Sue Chih H
Subject: NDA 22287

Hi Stella:

Please kindly assist us in a simple statistical analysis.

For the May 30, 2008 amendment, the sponsor submitted the following data.

In the combined phase 1 and 3 studies, 37% (75/202) and 75% (3/4) of the EMs and PMs (CYP2C19 genotypes), respectively, experienced at least treatment-emergent AE.

Is there a statistically significant difference between EMs and PMs? A statistical association between CYP2C19 genotype and AE?

It seemed to me that there is no statistical association between CYP2C19 genotype and AE.

Please kindly comment.

Thanks,

Jane

Appears This Way On Original

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

NDA/BLA Number: Applicant: Stamp Date:
Drug Name: dexlansoprazole NDA/BLA Type:22287 Dec 31, 2007

On initial overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		No	The to-be-marketed formulation was used for the clinical trials
2	Has the applicant provided metabolism and drug-drug interaction information?	Yes		
Criteria for Assessing Quality of an NDA				
Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	yes		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA
Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	Yes		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	Yes		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?	Yes		
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	Yes		
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		No	The firm submitted waiver request for 0-1 month old and deferral for 0-11 months old, 1-11 years old, and 12-17 years old.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		No	NA
11	Is the appropriate pharmacokinetic information submitted?	Yes		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes		
General				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR A NEW NDA/BLA**

13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	Yes		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	Yes		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	Yes		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes		
17	Was the translation from another language important or needed for publication?		No	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

PeiFan (Jane Bai)

Feb 14, 2008

Reviewing Pharmacologist

Date

Sue Chi Lee

Feb 14, 2008

Team Leader/Supervisor

Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Checklist for a New NDA_BLA 110307

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this page is the manifestation of the electronic signature.**

/s/

Jane Bai
12/1/2008 09:59:13 AM
BIOPHARMACEUTICS

Kristina E Estes
12/1/2008 10:00:51 AM
PHARMACIST

Sue Chih Lee
12/3/2008 09:37:46 AM
BIOPHARMACEUTICS

25 Page(s) Withheld

√ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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this page is the manifestation of the electronic signature.**

/s/

Patrick Marroum
12/16/2008 04:09:27 PM
BIOPHARMACEUTICS